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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1947

## ORIGINAL ARTICLES

### THE UNRELIABILITY OF CYANOSIS IN THE RECOGNITION OF ARTERIAL ANOXEMIA\*

BY JULIUS H. COMROE, JR., M.D.

AND

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IN 1919 Stadie<sup>7</sup> first correlated arterial oxygen saturations with clinical impressions of cyanosis in patients with pneumonia. His data show that lower arterial oxygen saturations were usually associated with more intense cyanosis but that the arterial saturations corresponding to impressions of slight, moderate, marked and intense cyanosis varied widely in different patients. In 12 patients with "moderate cyanosis," the arterial oxygen saturations ranged from 65 to 91% while in 12 instances of "marked cyanosis," the saturations varied from 56 to 86%. A few years later, Lundsgaard and Van Slyke,<sup>5</sup> in their monograph, "Cyanosis," summarized the factors which contribute to the presence of cyanosis and concluded that approximately 5 gm. of reduced hemoglobin must be present in 100 cc. of capillary blood to produce visible cyanosis in an individual otherwise normal; this could correspond to an arterial oxygen saturation of 80% and a venous saturation of 55% (assuming a peripheral A-V oxygen difference of 5 vols. per 100 cc.). An arterial oxygen

saturation of 80% is equivalent to that produced by inhalation of 10 to 12% oxygen instead of the normal 21% present in room air.

Despite these 2 careful studies which indicated that serious arterial anoxemia may exist before even moderate cyanosis is visible, most physicians have continued to regard cyanosis as the most characteristic sign of anoxemia and the most reliable guide for intelligent oxygen therapy.<sup>2</sup> It has been our impression for some years that excellent diagnosticians differ widely in their ability to recognize visually the presence of arterial anoxemia. The development of the oximeter by Millikan<sup>6</sup> provided us with a new method with which we could repeat and extend earlier studies<sup>7</sup> using large numbers of observers and subjects. It became evident early in these studies (a) that the detection of cyanosis depends not only upon variables in the patient,<sup>1,5</sup> but also upon variables in observers and (b) that cyanosis is a poor guide for the detection of arterial anoxemia of slight to moderate degrees.

\* This work was performed under contract with the Medical Division, Chemical Warfare Service, Edgewood Arsenal, Maryland.



**Method.** These experiments were designed to measure the highest arterial oxygen saturation at which observers could detect cyanosis. The arterial oxygen saturation of normal subjects was varied by the inhalation of low oxygen mixtures while observers attempted to estimate the existence and degree of cyanosis present. The arterial oxygen saturation was measured continuously by an oximeter. This instrument is essentially a miniature photo-electric colorimeter which may be placed on the ear; it measures arterial oxygen saturation with an average accuracy of 3% (as compared with values obtained by direct determinations on arterial blood). A total of 20 subjects (normal white males between the ages of 19 and 25, all accustomed to laboratory procedures) and 127 observers (105 medical students and 22 physicians) participated in the study.

A typical experiment was conducted as follows: An oximeter was attached to the subject's left ear. His nose was occluded by a clip. He then breathed through a mouthpiece, an inspiratory demand valve, and an expiratory flutter valve. Arrangements were made so that he might inhale room air, 100% oxygen, or 12, 10, or 8% oxygen (the remainder of the gas mixture in the latter 3 instances being nitrogen) in random sequence; precautions were taken that no one except the recorder knew the gas mixture being inhaled or the oximeter readings until the experiment was concluded. Five 6000 liter high pressure tanks containing the gas mixtures were connected to a 5 outlet manifold; the oximeter recorder, the gas tanks and all manipulations of these were obscured from the observers and subject by a screen. The subject was given room air to breathe, and the observers were informed that the subject's color at that moment represented his "normal" color.\* From this time on the observers, in groups of 4 to 10, were instructed to note the color of the subject's face, right ear, hands, fingers or nail-beds every  $\frac{1}{2}$  minute and independently record it as "normal," "slightly or questionably cyanotic" or "definitely cyanotic." Since each experiment lasted approximately 30 minutes, each observer made about 60 color estimations. During

this time the subject was given high and some of the low oxygen atmospheres to breathe for variable periods of time. Each subject was made anoxicemic at least twice in each experiment. Each low oxygen mixture was breathed for a minimum of 2 minutes after the oximeter had reached its lowest level.

The conditions under which the experiments were conducted were unusually favorable for early detection of cyanosis by the observer for several reasons: (a) the experimental room was lighted by daylight or by artificial tungsten filament lamps; (b) the subject's normal color was observed as a control with which ensuing color changes could be compared; (c) the observers were informed that periods of low and high arterial oxygen saturation in the subject could be expected during the ensuing 30 minute period; and (d) all subjects were white males.

The studies were conducted in a warm room, free from draughts, to minimize the occurrence of peripheral vasoconstriction and local cyanosis due to cold. Total hemoglobin was determined upon venous blood in 16 of 20 subjects; hemoglobin varied from 13.5 to 16.5 gm. per 100 cc.

**Results.** In Table 1 are recorded the levels of arterial oxygen saturation corresponding to estimations of "normal color," "slight or questionable cyanosis" and "definite cyanosis." This shows that the visual impressions of cyanosis are not necessarily accurate indications of anoxemia. Of the 3673 observations made when the subjects were breathing room air or oxygen and had oximeter readings of 96 to 100%, 26% stated that slight cyanosis existed. Furthermore only 49% of the students and 53% of the staff observations indicated "definite cyanosis" at the times when the oximeter registered 81 to 85% saturation (the level found by Stadie in severe lobar pneumonia).<sup>7</sup> Even at 71 to 75% saturation, 25% of the student and 15% of the staff observations recorded only "slight cyanosis."

The highest level of arterial oxygen

\* When the medical students acted as observers, a trial experiment was conducted first: The subject breathed 8 or 10% oxygen and the observers watched the development of cyanosis while the recorder called out the oximeter readings. When all observers recognized definite cyanosis, the subject breathed 100% oxygen and the observers were then permitted to observe the abrupt color change from blue to pink.

saturation at which each observer noted definite cyanosis is recorded in Table 2. Because of the marked inconsistencies that occurred in the records of many observers, data from consistent "series" only are included in this table.\* The median in both the student and staff groups noted definite cyanosis at 85 to 81% saturation.

For example, 1 physician first noted definite cyanosis at levels of 84, 77, 94 and 82% in 4 consecutive trials upon the same subject within a period of 40 minutes. There were 35 cases in which observers noted definite cyanosis (in consistent series) 2 to 5 times in the same subject. In 11 instances (31%) the highest and

TABLE 1.—PERCENTAGES OF TOTAL OBSERVATIONS AT VARIOUS ARTERIAL OXYGEN SATURATION LEVELS NOTED AS NORMAL COLOR, SLIGHT CYANOSIS OR DEFINITE CYANOSIS

Oximeter reading (arterial O <sub>2</sub> saturation)	No. observations at each arterial O <sub>2</sub> level			% observations reported								
				Normal color			Slight cyanosis			Definite cyanosis		
				Students (%)			Students (%)			Students (%)		
	Students	Staff	Total	Students	Staff	Total	Students	Staff	Total	Students	Staff	Total
100-96 . . .	2865	808	3673	67	70	68	27	22	26	6	8	6
95-91 . . .	711	203	914	42	48	43	42	32	40	16	20	17
90-86 . . .	712	182	894	33	25	32	36	43	37	31	32	31
85-81 . . .	799	244	1043	15	10	14	36	37	37	49	53	49
80-76 . . .	418	76	494	10	4	10	43	29	40	47	67	50
75-71 . . .	139	47	186	4	0	3	25	15	22	71	85	75
Total . . .	5644	1560	7204									

TABLE 2.—HIGHEST LEVEL OF ARTERIAL OXYGEN SATURATION AT WHICH DEFINITE CYANOSIS WAS NOTED BY EACH OBSERVER WHO MADE 1 OR MORE SERIES OF CONSISTENT OBSERVATIONS.

Oximeter reading (arterial O <sub>2</sub> saturation)	Students	Staff	Total
100-96 . . . .	1	..	1
95-91 . . . .	9	2	11
90-86 . . . .	15	5	20
85-81 . . . .	19	7	26
80-76 . . . .	9	2	11
75 or below . .	18	2	20
	71	18	89

It must be remembered that the data in Table 2 represent the *highest* saturations at which observers detected definite cyanosis. An observer often noted cyanosis at a high level in 1 series of observations and 10 to 20 minutes later was unable to detect cyanosis in the same subject until a much lower oximeter reading was reached.

lowest levels at which the observer first noted cyanosis varied by 5% saturation or less, and in 13 of the other 24 instances the variation was 10% saturation or more. The highest and lowest levels at which definite cyanosis was first noted could not be determined accurately in all of the experiments. However, 20 observers (see Table 2) did not detect definite cyanosis until the oximeter readings fell below 75% saturation. On the other hand, 11 observers noted (in "consistent series") definite cyanosis at saturations above 90%. The validity of the observations at the higher levels may be questioned since none of the sudden "switchbacks" to 100% O<sub>2</sub> occurred when the saturations were above 90%; hence these observations were not so rigidly controlled as those in the 70 to 90% range, in which the ability to

\* A "series" is defined as the observations during a consecutive sequence of high oxygen, low oxygen and high oxygen inhalation. "Consistency" of an observer for a series was judged by the following criteria: (a) the observer must have noted "normal color" throughout the period that the subject was breathing room air or 100% O<sub>2</sub>; (b) if the observer recorded slight or definite cyanosis at some time after the subject inhaled a low oxygen mixture and the oximeter reading started to fall, he must have consistently recorded cyanosis until the subject breathed a mixture richer in oxygen and the oximeter readings rose; and (c) the observer must have noted later in the same experiment an abrupt change from "cyanosis" to "normal color" within 1 minute after the subject suddenly breathed 100% O<sub>2</sub> (following 12, 10, or 8% oxygen) and the oximeter readings rose to 95% or more.

note a sudden change from cyanosis to normal color aided in determining the "consistency" of each series.

There were also marked variations in the ability of different observers to detect cyanosis in any one subject. One observer noted definite cyanosis at a level of 94% saturation while a second physician, observing the same subject simultaneously, could not detect definite cyanosis until the oximeter fell to 71%, a difference of 23%. Differences of this type were noted in observations made upon each of the 20 subjects; these ranged from 3 to 23% (median 12%).

Though all the subjects were white males, cyanosis was not detected at the same level in all. It is impossible to state the average level at which cyanosis was observed in the different subjects, since some observers did not detect cyanosis at the lowest level of oxygen saturation reached in each series. It was evident though that the majority of observers could detect cyanosis at a level of 85% saturation or more in some subjects, but not until a level of 75% saturation or less in others. More quantitative information is available from an analysis of the number of "consistent series" noted in each subject. Upon 1 subject, no consistent observations were made by 7 observers (2 series each); in another, 11 "consistent series" were recorded by 7 observers out of a total of 14 series. In 4 subjects, 25% or less of the series were consistent; in 3, more than 50% of the series were "consistent." Our data indicate that few physicians make consistent observations on every trial. Of those observers who participated in only 2 series, 23% were consistent in both, of those in 3 series, 20% were consistent in all 3, in 4, only 13% were consistent throughout, while of those who had 5 trials, no observer was consistent in all.

The value of the notation "slightly cyanotic" is questionable for the following reason: 55% of 255 series of observations by medical students and 53% of 89 series by physicians were "inconsistent." The most frequent inconsistency was in cri-

terion "a" (see page 3); when the subjects were breathing room air or 100% O<sub>2</sub>, observers noted slight (usually) or definite cyanosis in 44% of the series.

Repeated practice by 1 individual in observing cyanosis over a period of 1 month did not enable her to detect definite cyanosis at higher levels of oxygen saturation or to become more consistent in her observations. Furthermore, those observers who participated in many trials were not significantly more consistent than those who participated in only 2, and the physicians as a group were no more consistent or able observers than were the inexperienced students.

There was no correlation in these experiments between the subject's total hemoglobin and the ability of observers to detect cyanosis early or consistently. However, no anemic or polycythemic subjects were included in this study (all the hemoglobins were above 13.5 and below 16.5 gm. per 100 cc.).

**Discussion.** Lundsgaard and Van Slyke<sup>5</sup> defined cyanosis as the blueness of the skin, mucous membranes or organs caused by changes in capillary blood (usually the presence of unusual amounts of reduced hemoglobin). In their opinion the most important factors which modify the perception of cyanosis are; (a) the thickness, color and opacity of the skin or membrane overlying the capillaries, (b) the number and length of blood filled capillaries in a given surface area, and the state of dilatation or constriction of the arterioles, capillaries or venules under observation, (c) variations in plasma color caused by dyes or drugs, and (d) variations in the type, color and amount of hemoglobin (presence of methemoglobin, sulfhemoglobin or carboxyhemoglobin).

The factors mentioned by Lundsgaard and Van Slyke are concerned with variables in the patient. We believe that an equally important variable is the wide range in the abilities of observers to detect cyanosis in any one patient. On the basis of our experiments, we can infer that very few physicians are capable of detecting slight degrees of arterial anox-

emia by the perception of surface blueness. It is probable that an extremely small percentage of physicians could be expected to diagnose early cyanosis in every case. In the majority of cases, arterial anoxemia is probably unrecognized until the saturation of hemoglobin with oxygen has fallen below 85%; in some it is unrecognized even at the 70 to 75% level.

It may be argued by those physicians who consider themselves highly skilled in the detection of cyanosis that most of our observers were relatively inexperienced medical students. It should be emphasized that the students had a preliminary trial in order to acquaint them with the color to be expected at each level of oxygen saturation in the particular subject under observation. Actually the students were only slightly less consistent in their estimations than was the physician group, which included physician anesthesiologists, and cardiologists who had wide experience in the detection of cyanosis. Furthermore the median observers noted definite cyanosis at the same level in both groups. In addition, conditions were particularly favorable for the recognition and recording of cyanosis at high levels of arterial oxygen saturation: the presence of good lighting, the opportunity to observe normal control color in each subject, the use of all young white male subjects, the awareness that a color change was imminent, and the use of a continuous method of measuring oxygen saturation, so that better correlation was obtained.

Another possible criticism of these experiments is that oximeter readings were employed instead of actual figures obtained by direct analysis of arterial blood. The oximeter has an average error of 3%; in the saturation range 75 to 100%, the limit of error is 5% and in the range 50 to 75% it is 8%. However, this error is not a systematically high or low one and

should cancel out in a large series of observations. The oximeter has the advantage of continuous recording so that the saturation of arterial blood can be known at the instant that cyanosis is recorded; this favors the recording of cyanosis at higher levels of arterial saturation.

It should be emphasized that not only is cyanosis frequently an unreliable guide to slight to moderate arterial anoxemia, but also other commonly used signs, such as rapid pulse and hyperpnea are not trustworthy. Dripps and Comroe studied the effects of breathing low oxygen mixtures for 8 minutes upon the circulation and respiration of normal subjects. They found that the inhalation of 18% O<sub>2</sub> led to an average increase in pulse rate of only 4%, 16% O<sub>2</sub> to 8% increase, 14% O<sub>2</sub> to 6% increase, 12% O<sub>2</sub> to 16% increase and 10% O<sub>2</sub> to 30% increase. These low oxygen mixtures corresponded to average arterial oxygen saturations of 94, 91, 89, 81 and 73% respectively. In the same experiments<sup>4</sup> respiration was not increased measurably by arterial anoxemia until 10% O<sub>2</sub> was inhaled. At this point, respiratory minute volume increased only 16% (average arterial saturation 73%). Although data obtained from such brief exposures to low oxygen concentrations do not necessarily apply to clinical anoxemia, they suggest that slight anoxemia produces effects upon circulation and respiration which could escape even careful clinical observations. In some individuals the respiratory and circulatory responses are absent or poor even with moderate degrees of anoxemia.

Although other signs (mental confusion, delirium) have been suggested as indications for oxygen therapy, they do not represent early changes. In our experience, the extent of arterial anoxemia can be determined accurately in patients only by direct analyses of arterial blood.\*

\* The oximeter at present cannot be employed to indicate the level of arterial oxygen saturation in cyanotic individuals since the instrument must be "set" for each individual at a *known* value. In an individual known to be normal, the oximeter is "set" at 95 to 98% if the individual is breathing room air or at 100% if breathing oxygen. In a cyanotic patient, an arterial puncture can be performed, a determination of oxygen saturation can be done quickly by the method of the Van Slyke and Neill,<sup>5</sup> and the oximeter can then be "set" to this figure. An evaluation of therapy can then be made easily by noting oximeter changes in response to the employment of oxygen by oropharyngeal catheter, tent, mask or by pressure breathing.

Furthermore, our data indicate that this is the only way in which slight to moderate degree of anoxemia can be detected.

In present practice of medicine, every effort is being made to place therapy upon a scientific basis. It is often essential to know blood sulfonamide, penicillin and salicylate levels in order properly to evaluate therapy. Yet in the evaluation of arterial anoxemia, the clinician still uses a relatively insensitive and unreliable guide, namely cyanosis. The methods for determining arterial oxygen concentration are well established. Arterial puncture is neither dangerous nor painful if done carefully. It is suggested that oxygen therapy be put upon a more quantitative basis by measuring arterial saturation in patients suspected of being anoxicemic and by employing doses or concentrations of oxygen sufficient to increase arterial saturation to normal levels. More frequent measurements of arterial oxygen saturation by direct means (in patients suspected of being anoxicemic) should result in the elimination of much unnecessary oxygen therapy. It will also result frequently in the correction of concentrations of oxygen being given to those in need of oxygen.

Oxygen therapy is of value in many cases of anoxemia. The patient who is chronically anoxicemic usually develops certain compensatory changes which permit a relatively normal existence at rest without the need for oxygen administration. However, the recovery of an *acutely* anoxicemic patient (who often has fever and accelerated metabolism) can be hastened by maintaining normal amounts of oxygen in the blood. It is doubtful if

oxygen therapy *per se* cures disease processes. However, it is of great value as supportive therapy in anoxemia and there it should be used more quantitatively. When oxygen is given in high concentrations in the treatment of conditions unassociated with anoxemia<sup>3</sup> (e. g., in coronary occlusion, etc.), determinations of arterial oxygen saturation are unnecessary since the arterial blood is almost completely saturated before oxygen inhalation is begun.

**Summary and Conclusions.** 1. The ability of observers to detect cyanosis was evaluated by comparing their color estimations with known arterial oxygen saturations (oximeter).

2. The majority of 127 observers were unable to detect the presence of definite cyanosis until the arterial oxygen saturation fell to approximately 80%; 25% of observers did not note definite cyanosis even at arterial saturation levels of 71 to 75%.

3. There were marked variations in the ability of an observer to note cyanosis in different subjects or even in the same subject at different times. There were wide variations in color estimations when 5 to 10 observers watched cyanosis develop in the same subject at the same time.

4. The detection of cyanosis is dependent not only upon variable factors in the patient but also upon the ability of individual observers to note color changes.

5. Visual impressions of cyanosis are unreliable. Serious grades of arterial anoxemia may be unrecognized by many physicians unless arterial blood is obtained and analyzed for oxygen content and capacity.

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## PHLEBOGRAPHY FOR THE STUDY OF OBSTRUCTION OF THE VEINS OF THE SUPERIOR VENA CAVAL SYSTEM\*

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PHLEBOGRAPHY, by providing Roentgen visualization of the veins, offers a method unequalled by other techniques for defining and localizing lesions of the veins and determining the distribution of the collateral circulation. This method has been used mainly in connection with thrombosis of the veins of the lower extremity. Its importance in similar lesions of the veins of the superior vena caval system has not been emphasized. Some reports on diseases of the superior vena cava<sup>4</sup> and of the subclavian and axillary veins<sup>7,8</sup> have included phlebographic studies. There has been no report which offers a full appraisal of the value and limitations of phlebography in cases of obstruction of the superior vena cava and its main tributaries. It is our purpose, therefore, to present cases which are illustrative of our experience in lesions of this type, and which provide adequate testimony to the value of phlebography as a means for precise diagnosis.

**Technique.** The technique of phlebography in the superior vena caval system is quite simple. The sites usually employed for injection of the contrast medium are the external jugular vein and the median basilic vein. For lesions of the superior vena cava or innominate vein, the external jugular is preferred, although when this vein is not accessible, the veins of the antecubital fossa may be used. In lesions of the subclavian, axillary, or brachial veins, the median basilic is selected. Use of other veins in the ante-

cubital fossa, particularly the cephalic, may lead to errors in interpretation when the obstruction occurs solely in the axillary or brachial veins. This is made obvious by reference to Figure 8. The cephalic vein enters the axillary vein at a point close to the subclavian, so that obstruction in the axillary or brachial vein will not be visualized.

The materials we have used for phlebography are Thorotrast, 35% Diodrast and 70% Diodrast. Some objection has been raised to Thorotrast because it is radioactive and remains in the cells of the reticulo-endothelial system for a long time. We have never observed any disagreeable effect from the use of the small amounts of Thorotrast necessary for phlebography. Diodrast is equally useful, however, is rapidly excreted by the kidney and does not carry the threat of radioactivity. Diodrast (35%) provides about the same density in phlebograms as Thorotrast, while 70% Diodrast gives greater contrast and is therefore preferable for visualization of the innominate vein or superior vena cava. To obtain a phlebogram of the superior vena cava or its tributaries, the patient is placed on the cassette in the supine position. Regardless of the site of the injection of the contrast medium, the venipuncture is made in the usual way with a needle of 15 to 18 gauge. The injection is made uninterruptedly and as rapidly as possible. When it is intended to visualize the innominate vein or superior vena cava, 30 cc. of the contrast medium is used, and the injection must be rapid. In all other instances, 15 cc. suffices, and speed of injection is less important. The Roentgen ray film is exposed at the moment that the injection is

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completed. The target distance is 36 inches, and the technique is the same as for a chest film<sup>3</sup> with the exception that the time of exposure is doubled.

In the superior vena caval system, the only major vein which is not accessible to phlebography is the internal jugular. The procedure has relatively little use for investigation of the veins of the forearm.

those without a demonstrable mediastinal mass, the cause remains obscure.

When the superior vena cava is obstructed, the location and extent of the collateral circulation depend upon the site, duration and completeness of the obstruction. With occlusion of the superior vena cava above the point of entrance of the

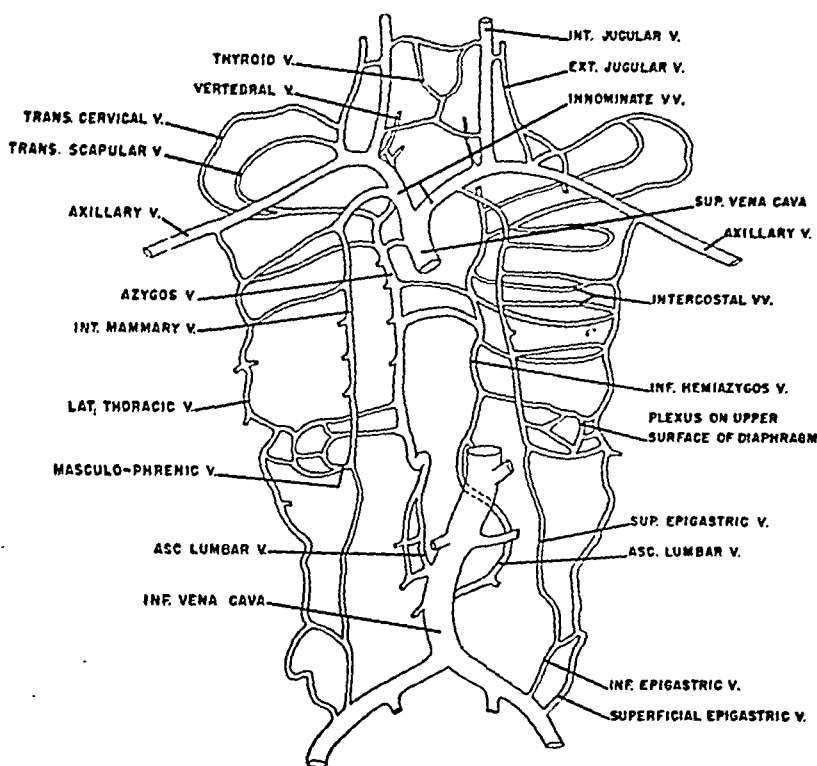


FIG. 1.—The collateral circulation in cases of superior vena caval obstruction. (After Blasinghame.)

**OBSTRUCTION OF THE SUPERIOR VENA CAVA.** Obstruction of the superior vena cava may be complete or incomplete. The etiology is the same in both instances. In our experience<sup>4</sup> the main causes have been, in order of frequency, aortic aneurysm, bronchogenic carcinoma, and mediastinal lymphoma. Less frequent causes are metastatic carcinoma of the mediastinal lymph nodes, thrombosis of the superior vena cava and mediastinitis. In a small percentage of cases, especially

azygos vein, this vein and its tributaries are the main collateral channels and therefore the visible collateral circulation is not extensive. A few dilated veins may be seen in the neck, shoulder regions and upper part of the chest. In contrast, when the obstruction is below the azygos vein, an extensive collateral circulation is visible on the chest and abdomen, representing the routes whereby blood from the superior vena caval system is transported to the inferior vena cava for return to

the heart (Fig. 1). The longer the duration and the more complete the degree of obstruction, the more extensive the collateral circulation will be.

The use of phlebography in the diagnosis of complete obstruction of the superior vena cava is exemplified in the following case.

**Case Reports.** CASE 1. R./B. (B50005) was a 60 year old Negro who had a malignant lymphoma of the superior mediastinum. He had dyspnea, slight facial edema, dilated veins of the chest and neck, and generalized lymphadenopathy. The venous pressure was 480 mm. of saline solution in the right arm, 450 mm. in the left arm, and rose to about 600 mm. in each arm with the "exercise test," which consists of having the patient forcefully open and clench the fist for 1 minute while the venous pressure is being measured.<sup>9</sup> The femoral venous pressure was 120 mm. A phlebogram made by injecting Diodrast into the right antecubital vein, clearly demonstrates the point of obstruction in the superior vena cava and the extent of the collateral circulation (Fig. 2, A and B).

Ordinarily the results of phlebography are more satisfactory in this type of case when the injection is made into the external jugular vein. When the median basilic vein is used, the superior vena cava often is not visualized, and the phlebogram may show only the collateral circulation (Fig. 3).

An example of incomplete obstruction of the superior vena cava is shown in Figure 4, A and B. These represent the phlebogram of a patient with an aneurysm of the ascending limb of the aorta.

**OBSTRUCTION OF THE INNOMINATE VEIN.** The etiology of innominate vein obstruction is essentially the same as for obstruction of the superior vena cava and may also be complete or incomplete. In the innominate vein thrombosis is probably more frequent than in the superior vena cava. This is explicable by the fact that thrombi in the subclavian vein may extend into the innominate but rarely go farther. The left innominate vein is more often obstructed by aneurysm of the aorta

than the right, mainly because of the intimate relationship which the left innominate bears to the aortic arch.<sup>3</sup>

When an innominate vein is obstructed, the blood is returned to the heart from the obstructed side principally by way of the other innominate. The route follows collateral veins which traverse the midline and include all of the tributaries of the innominate, jugular and subclavian veins (Fig. 1). Judging from our experience with phlebograms, however, the subclavian and internal jugular veins are usually quite dilated, and their tributaries, especially those of the internal jugular, are a prominent part of the collateral circulation.

Figure 5, A and B, and Figure 6, A and B, represent the phlebograms in a case of complete obstruction of the right innominate vein and partial obstruction of the superior vena cava.

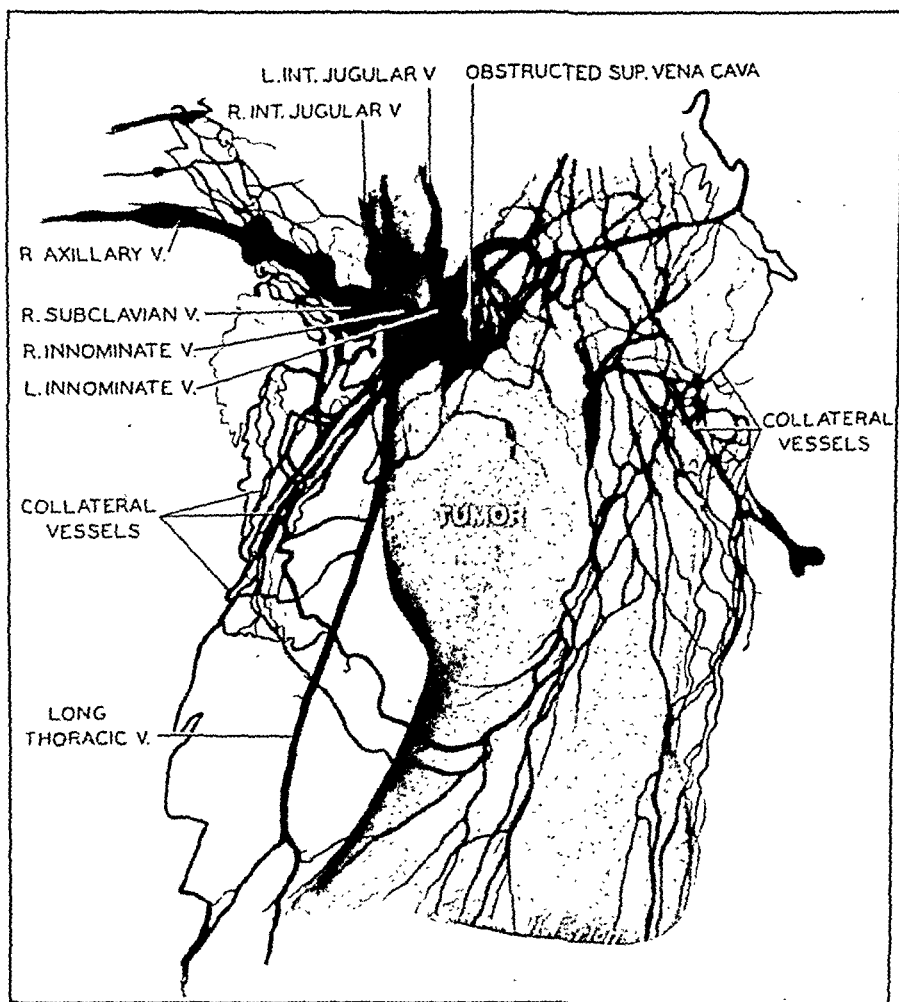
CASE 2. This patient (C13989) was a 64 year old colored male, who was first admitted to the hospital in 1939 with the picture of acute superior vena caval obstruction. No cause for the obstruction was found, and there was no demonstrable mediastinal tumor. A phlebogram was made by injecting Thorotrast simultaneously into the veins of both arms. This showed dilatation of both axillary veins but the remainder of the superior vena caval system was not visualized. The venous pressure in the arms was 500 mm. of saline solution with a rise to 590 mm. with the "exercise test." The femoral venous pressure was 70 mm. After 2 months of hospitalization, the patient was improved, and at the time of discharge the venous pressure was 330 mm.

This patient returned to the hospital 6 years later with symptoms of prostatism which later was found to be due to carcinoma of the prostate and was treated by transurethral resection. At this time he still appeared to have evidence of obstruction of the superior vena cava, in the form of a prominent network of veins in the neck and over the chest and abdomen. Venous pressure measurements were as follows: right arm 273 mm., left arm 232 mm., femoral 50 mm. These findings in themselves merely indicated that there was obstruction in the





A



B

FIG. 2.—Phlebogram (A) and drawing (B) of a patient with complete obstruction of the superior vena cava due to mediastinal tumor. The point of obstruction and the extensive collateral circulation are shown.

superior vena caval system, but were of little value in localizing it. There was obviously more obstruction in the right side than on the left. Precise localization was obtained by means of phlebography. Figure 5 shows the phlebogram of the right side, made by injecting 30 cc. of 70% Diodrast into the right external jugular vein. The right innominate vein is not filled beyond its first part. The subclavian and internal jugular veins and their tributaries are greatly dilated

nate vein and partial obstruction of the superior vena cava, presumably due to long-standing thrombosis. The studies, including those of the first period of hospitalization, would seem to indicate that the process started in the superior vena cava and extended into the right innominate vein. The adjustment made by the patient to the venous obstruction has been excellent.



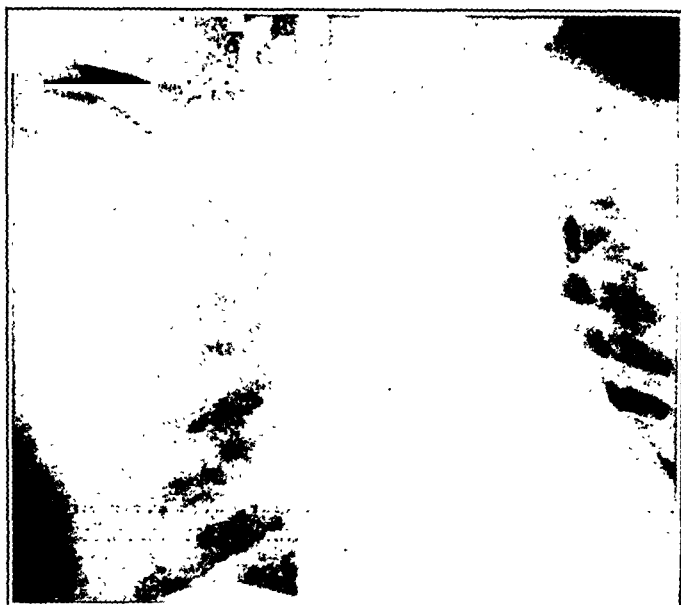
FIG. 3.—Phlebogram of a case of complete obstruction of the superior vena cava. The extensive collateral circulation is seen but the superior vena cava and its immediate tributaries are not visualized.

and have been filled by reflux of the contrast medium. Numerous collaterals cross the midline from the internal jugular to enter the left innominate vein. At the point where this vein enters it, the superior vena cava is somewhat narrowed. Figure 6, *A* and *B*, shows a similar study made on the left side. The left internal mammary, pericardiac and azygos veins are clearly a part of the collateral circulation.

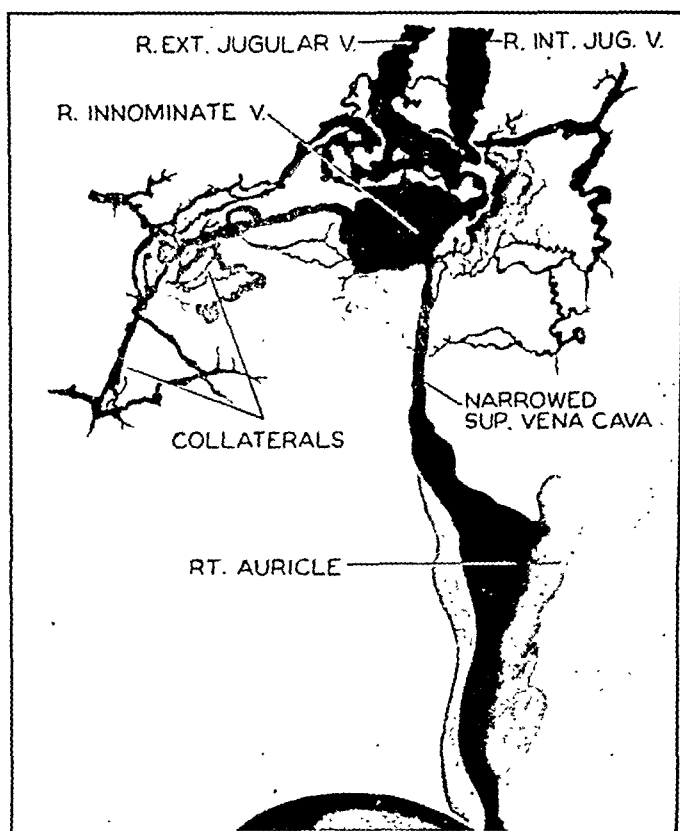
In summary, therefore, this patient had complete obstruction of the right innomi-

An example of complete obstruction of the left innominate vein is shown in Figure 7, *A* and *B*, the phlebogram of Case 3.

CASE 3. A 68 year old white male had obstruction of the left innominate vein due to metastatic carcinoma. The veins in the left pectoral region, left side of the neck and at the left shoulder were prominent. The left arm was slightly swollen. The venous pressure in this arm was 200 mm. of saline

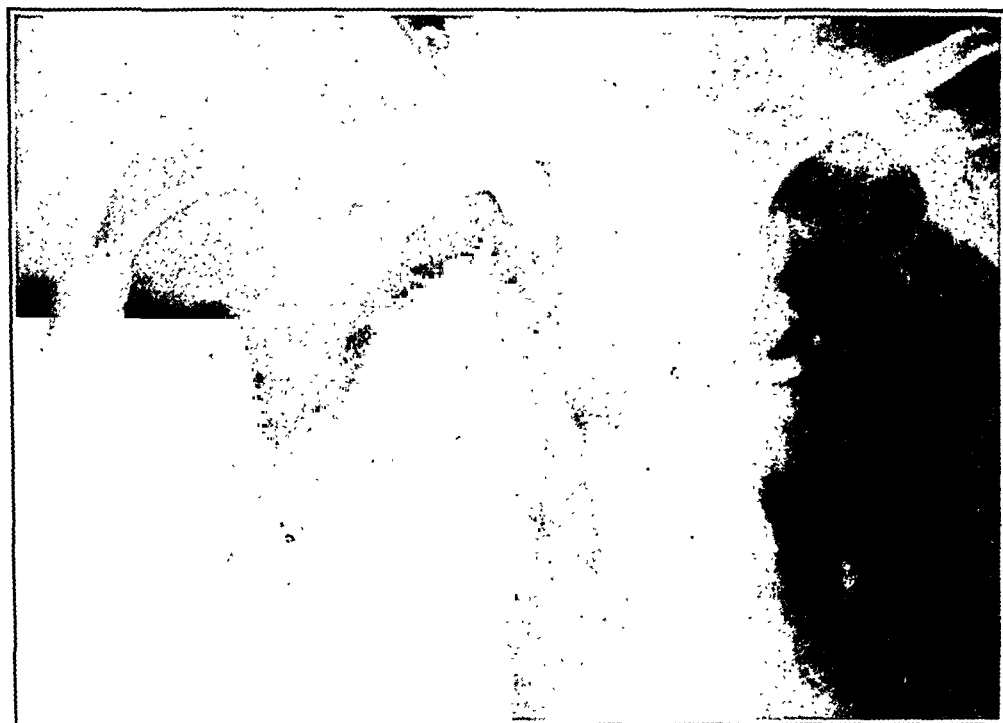


A

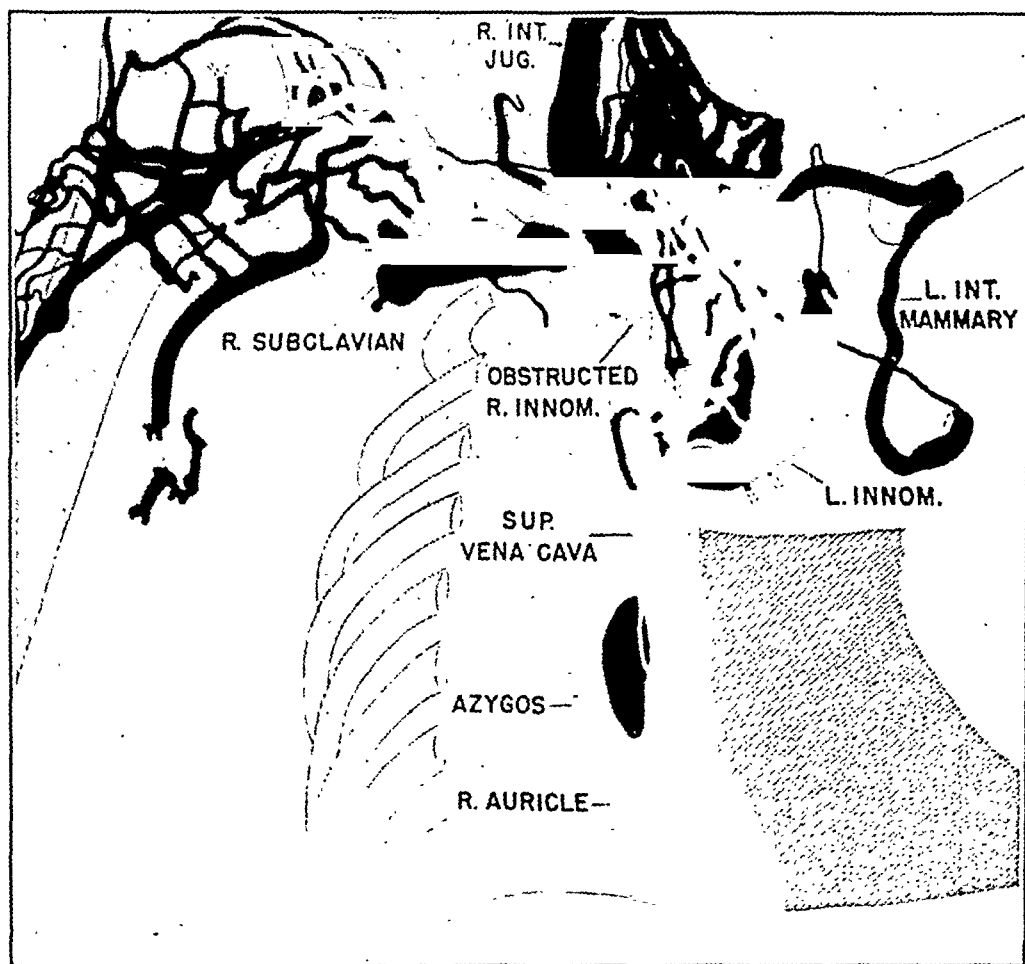


B

FIG. 4.—Phlebogram (A) and drawing (B) showing an incomplete obstruction of the superior vena cava due to an aneurysm of the aorta.



A



B

FIG. 5.—Phlebogram (A) and drawing (B) showing complete obstruction of the right innominate vein with filling of the left innominate and superior vena cava by way of collateral channels,

solution and rose to 280 mm. with the "exercise test." The venous pressure in the right arm was 130 mm. and did not change with the "exercise test." The phlebogram shows that the greater portions of the subclavian and innominate veins are occluded. The terminal portion of the left innominate vein is visualized at the point of junction with the right innominate and is greatly narrowed. The right internal jugular and innominate veins have been filled from the numerous collaterals which cross from the

congestive heart failure, trauma or effort, and constriction by scar tissue.<sup>8</sup> Incomplete obstruction of the axillary vein is a frequent sequel of radical mastectomy and has been shown to be due to angulation of the vein at the axilla.<sup>10</sup>

The development of collateral circulation depends upon the site of obstruction. When the first part of the axillary vein alone is occluded, the cephalic vein is the main collateral vessel. When the entire

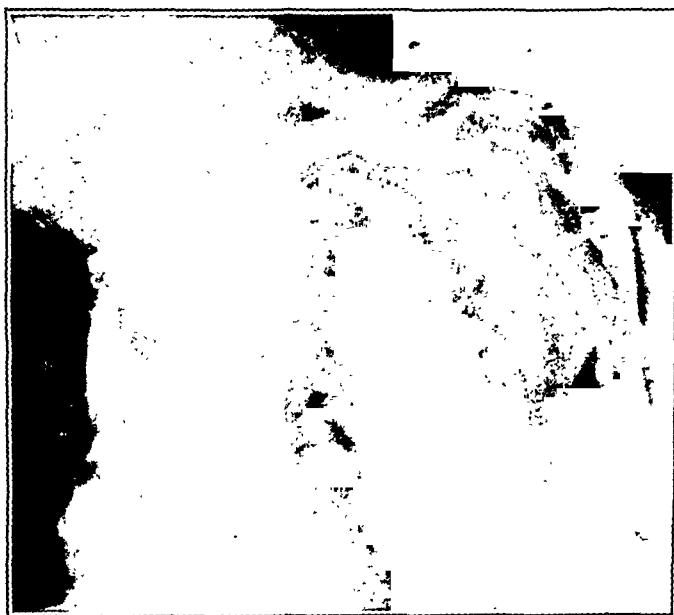


Fig. 6 A. (Legend on next page)

obstructed side. Autopsy examination in this case demonstrated metastatic carcinoma in the superior mediastinum. The left innominate and subclavian veins were obstructed due to invasion by the carcinoma. The primary site of the carcinoma was not discovered.

**OBSTRUCTION OF THE SUBCLAVIAN AND AXILLARY VEINS.** In contrast to the rarity of thrombosis as a factor in the obstruction of the innominate vein or superior vena cava, subclavian and axillary vein obstruction is commonly due to thrombosis and in the case of the subclavian, is usually complete. The causes for thrombosis in this location are, in the order of frequency, metastatic carcinoma,

axillary vein is obstructed, collaterals develop from minor branches of the basilic, brachial and cephalic veins to communicate with small veins of the neck and thorax, including the external jugular, long thoracic, costo-axillary, subscapular and intercostal veins. These veins return the blood to the heart by way of the subclavian, internal jugular and innominate veins. There is little communication with veins of the opposite side. In cases in which the subclavian vein alone is obstructed, the major collaterals develop from the tributaries of the axillary. In addition, tributaries of the basilic and brachial contribute. The collateral channels circumvent the obstruction and carry blood to

the jugular and innominate veins of the same side. When the axillary and subclavian veins both are obstructed, the collateral circulation is essentially the same as when the axillary vein alone is involved. The collateral network is more

CASE 4. The patient was a young white woman who fell backward and, in attempting to break the fall, caught her weight on her outstretched right hand. By the next day, she noticed weakness and fullness of the right upper extremity. The arm was

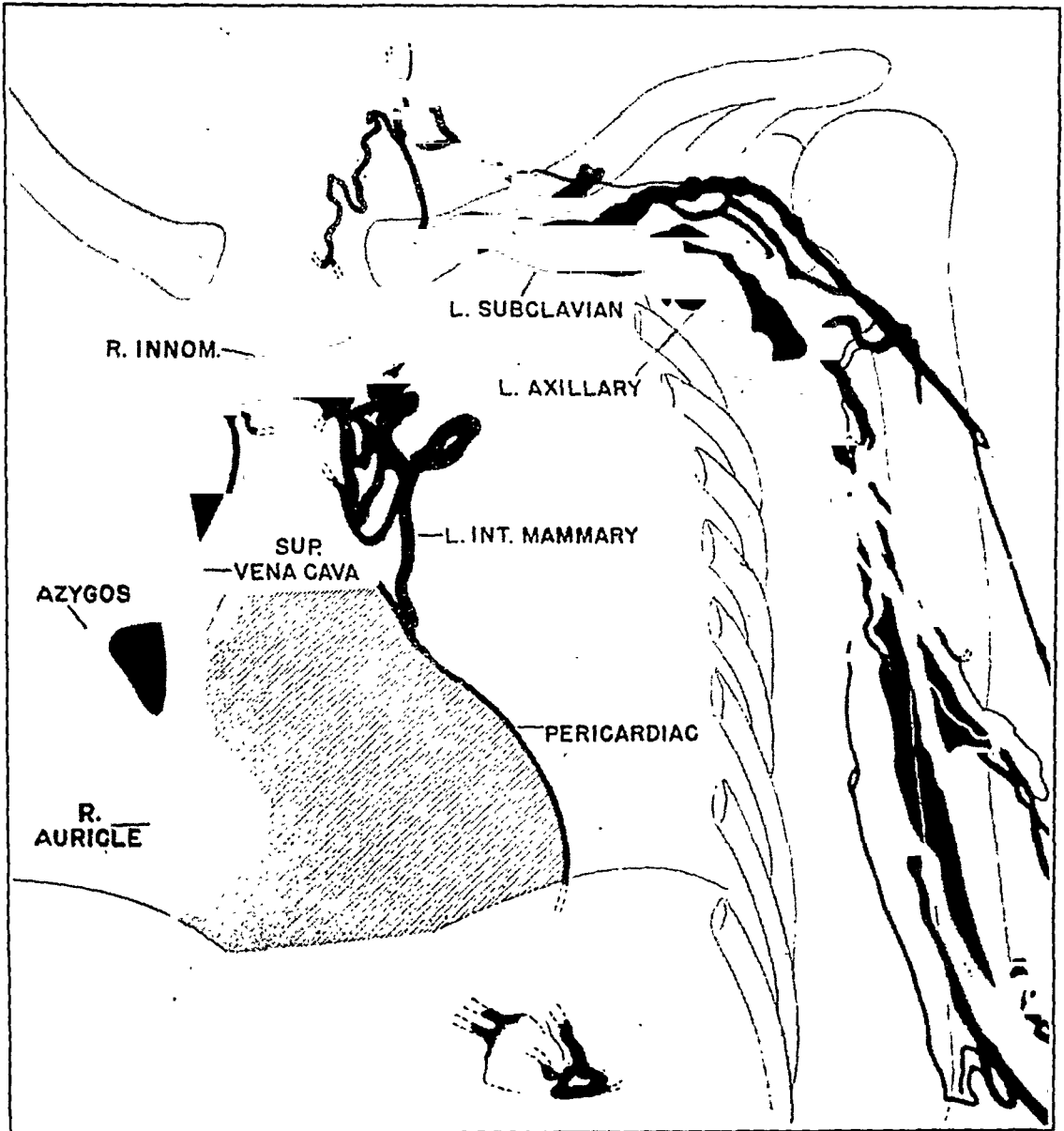


FIG. 6 B

FIG. 6.—Phlebogram (A) and drawing (B) visualizing the left innominate vein and its tributaries from the same case as in Figure 5. The superior vena cava is narrowed in its first part. In the drawing the vein labelled right innominate is the left innominate.

extensive, however, and the tributaries of the subclavian vein participate in the venous anastomosis.

An example of subclavian vein thrombosis due to trauma is shown in Figure 8, A and B, and Figure 9, A and B.

slightly swollen and cyanotic, and the veins were distended. The venous pressure in the right arm was 310 mm. and rose to 410 mm. with the "exercise test." The venous pressure in the left arm was 135 mm. At this time a phlebogram (Fig. 8, A and B) showed

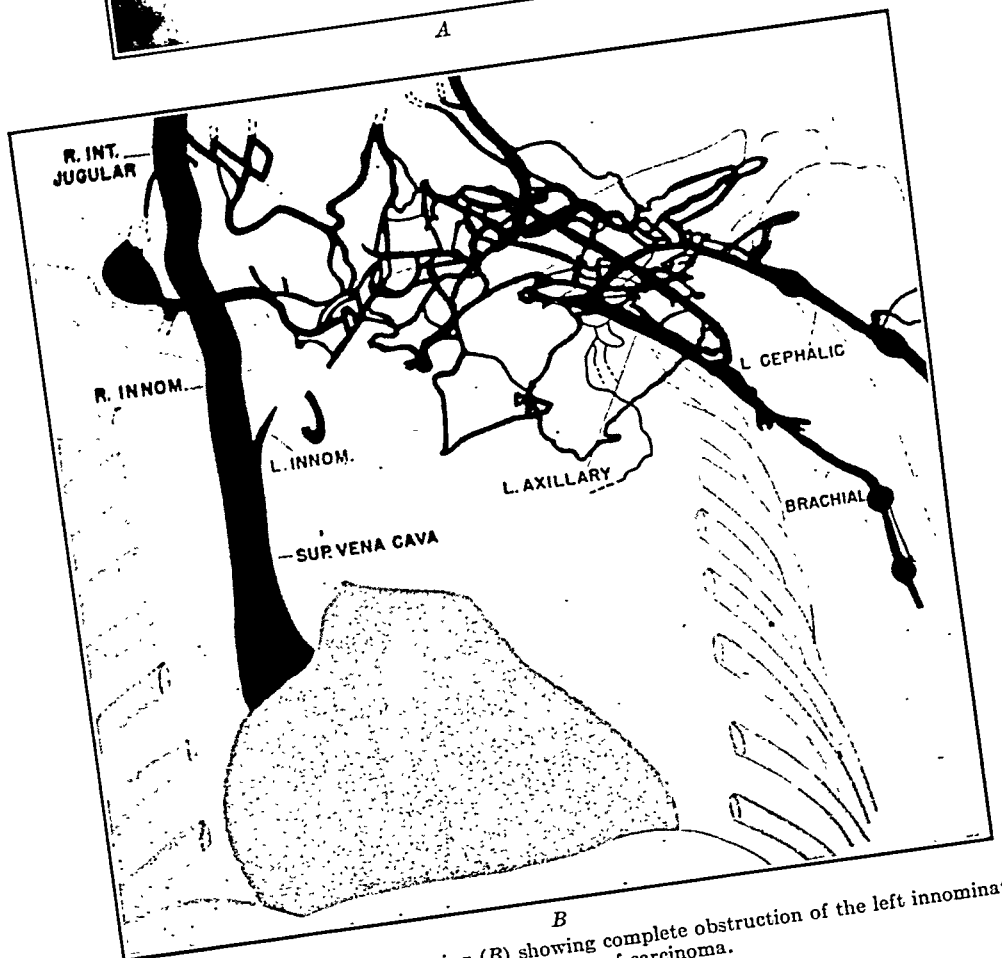
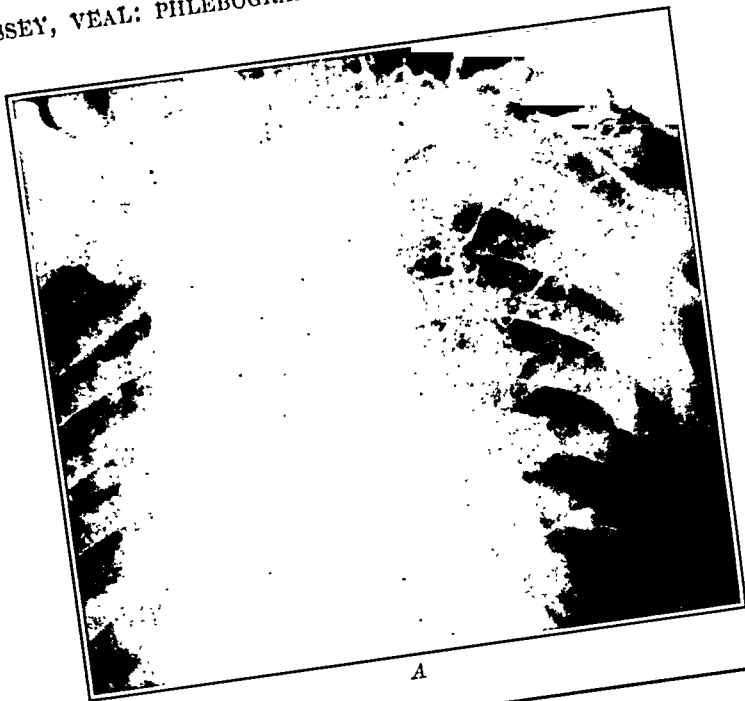


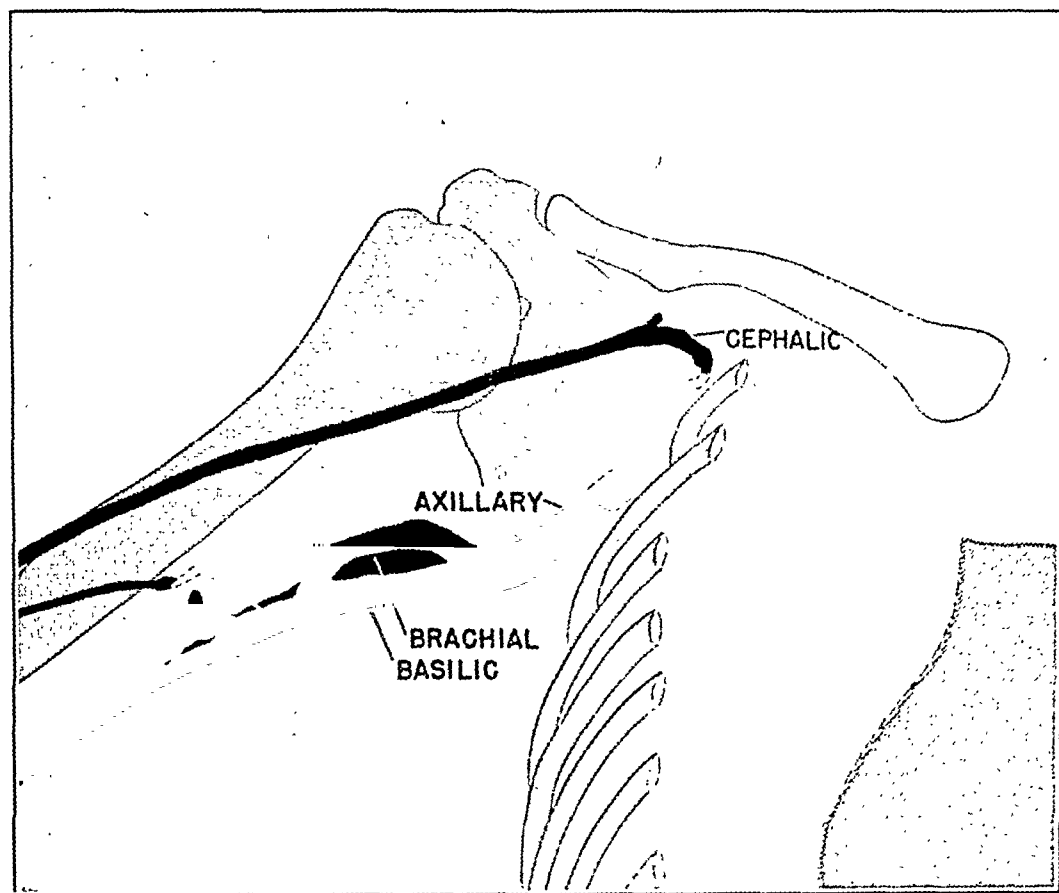
FIG. 7.—Phlebogram (A) and drawing (B) showing complete obstruction of the left innominate vein due to invasion of carcinoma.

dilatation of the brachial and axillary veins and filling of the cephalic vein which may have been retrograde or by way of collaterals in the arm. Figure 9, *A* and *B*, is from a phlebogram made 6 months later. It demonstrates a marked increase in the number of vessels with participation of branches

of the axillary, brachial, basilic and cephalic veins in the collateral circulation. At this time the patient was symptom-free, an extensive network of veins was seen at the pectoral region and shoulder, and the venous pressure was within normal limits but rose about 100 mm. with the "exercise test."



*A*



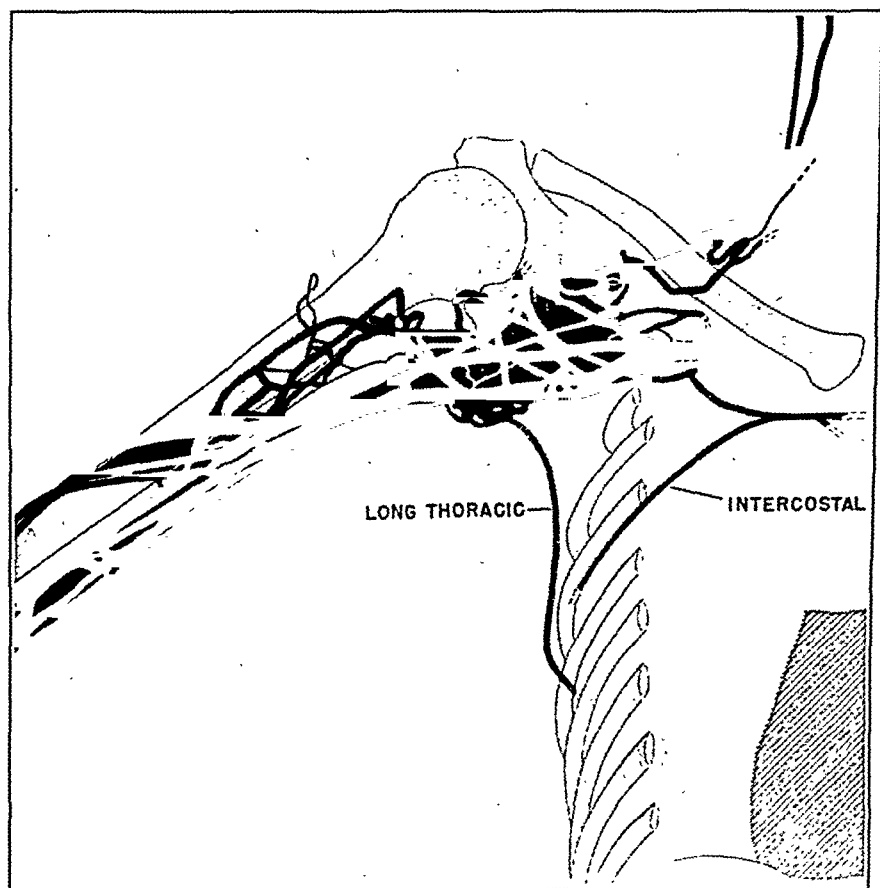
*B*

FIG. 8.—Phlebogram (*A*) and drawing (*B*) in a case of subclavian vein thrombosis due to trauma. The importance of the cephalic vein as a collateral channel is obvious.





A



B

FIG. 9.—Phlebogram (A) and drawing (B) of the same case shown in Figure 8 made 6 months later. The increase in the number of collateral vessels is shown.

Figure 10 represents a series of phlebograms showing the mechanism by which partial obstruction of the axillary vein may result following radical mastectomy. After this operation the angle at which the axillary vein enters the thorax when the patient's arm is in adduction may be so acute that the vein is obstructed. The obstruction is relieved when the arm is abducted.

that otherwise could be obtained only by dissection. For example, there is no other means to differentiate clinically obstruction of both innominate veins from occlusion of the superior vena cava, or axillary vein thrombosis from obstruction of the subclavian. There is no more accurate method for study of the development and extent of the collateral venous circulation.

One of the features which adds to the

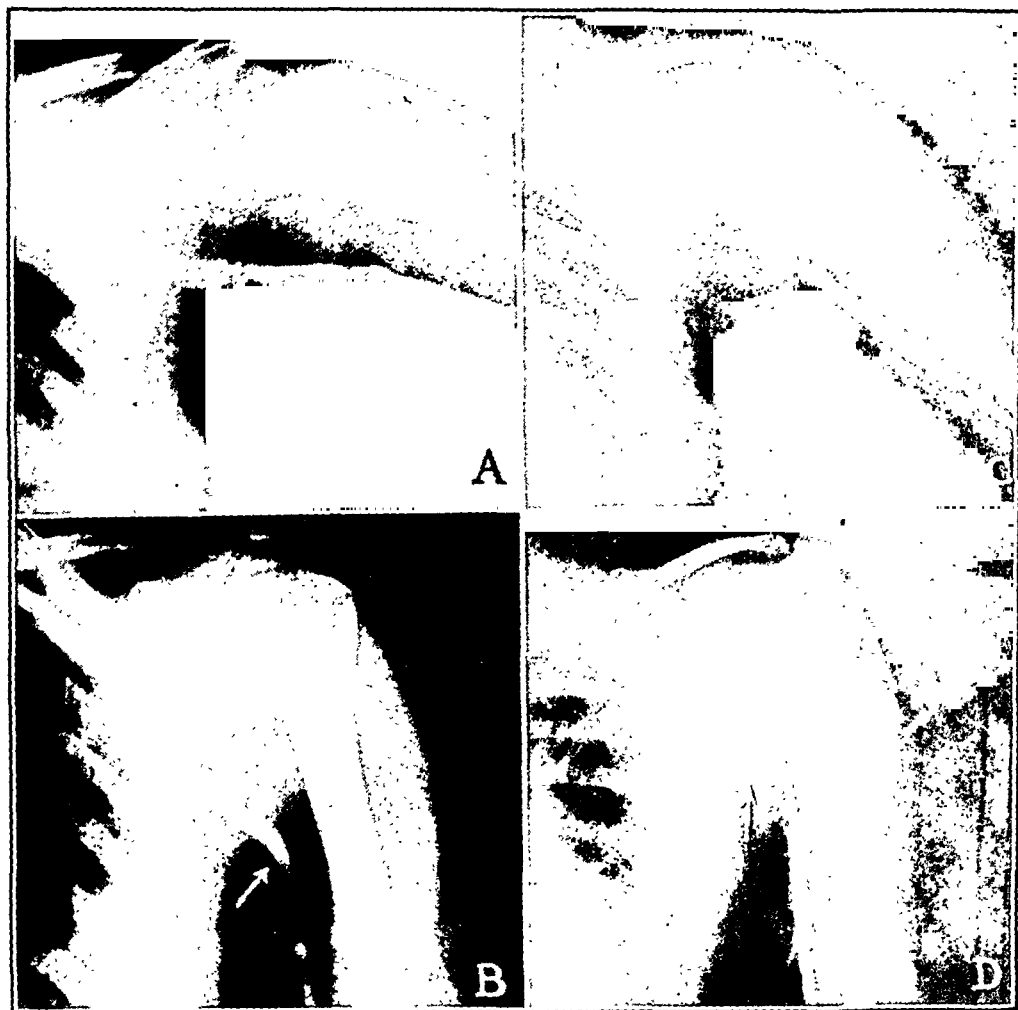


FIG. 10.—Phlebogram showing the mechanism of venous obstruction following radical mastectomy. A, Phlebogram showing normal axillary vein with arm abducted. B, Phlebogram of same patient with arm adducted. C, Phlebogram of axillary vein in a patient who developed edema of the arm only when the arm is dependent. Note that with the arm abducted the vein is not occluded. D, Phlebogram of the same patient with the arm adducted. Note complete occlusion of axillary vein (arrow) and backflow of opaque medium into tributaries.

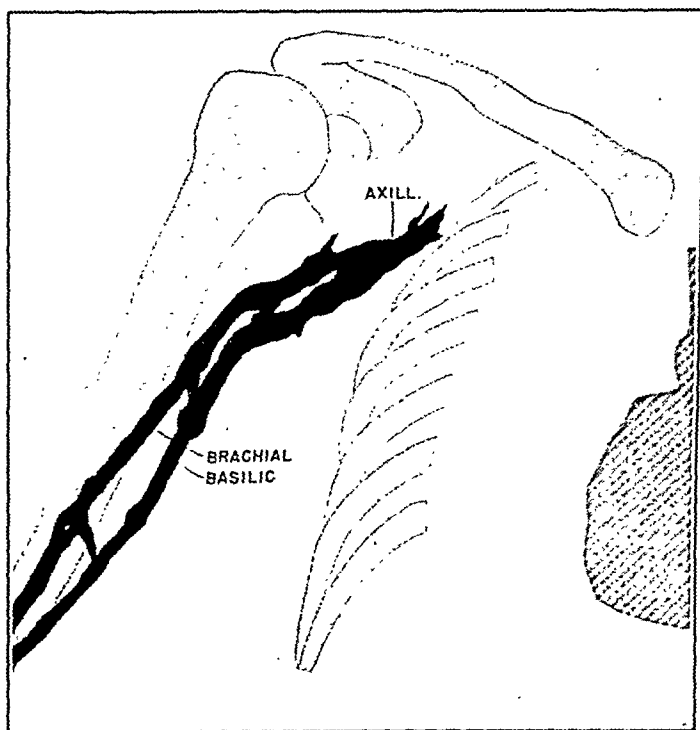
**Discussion.**—The results in the cases selected for presentation in this paper are typical of what may be expected in phlebographic study of obstructive lesions of the veins of the superior vena caval system. Phlebography provides anatomic details

attractiveness of phlebography of this type is its simplicity. No special apparatus is necessary, and the technique requires only the skill ordinarily employed in a venipuncture.

Phlebography with Diodrast is almost



A



B

FIG. 11.—Phlebogram (A) and drawing (B) in a normal patient. The film has been exposed when the contrast medium reached the subclavian vein giving the false impression of occlusion at this point.

entirely safe. Most patients experience a feeling of warmth in the face, extremities and rectum, while flushing of the face is also noted. These symptoms are mild and quite transitory, and require no treatment. Occasionally, there is brief nausea and vomiting. Less frequent toxic effects include pain along the course of the vein injected, urticaria, pruritus and a sense of constriction in the throat.

When urticaria and pruritus are especially disagreeable epinephrin gives prompt relief. Although we have never seen a serious reaction to Diodrast, there have been reported instances of severe hypersensitivity resembling anaphylactic shock.<sup>5</sup> It is advised that tests for hypersensitivity to the drug be performed before it is used.<sup>1,6</sup> This is not the place to debate whether or not Thorotrast is a safe drug for injection. We have used it many times for phlebograms and arteriograms before Diodrast was readily available, and have never seen a serious reaction, either immediate or remote, from its use for these studies. When either Diodrast or Thorotrast is accidentally injected outside a vein, local swelling and discomfort ensue. These effects are usually mild and temporary. Thorotrast remains indefinitely in the soft tissues, however, and causes a local fibroblastic reaction. We have never observed a case of phlebitis after the intravenous administration of either drug, although this complication has been recorded.<sup>2</sup>

The interpretation of phlebograms of the superior vena cava and its tributaries merely requires a superficial knowledge of anatomy. There is nothing like the difficulty encountered in attempts to interpret

phlebograms of the deep veins of the leg in which anatomic variation is frequent and ideal visualization is difficult to obtain. An error of interpretation may occur in phlebography of the superior vena caval system when the Roentgen ray film is exposed too soon. This will give a film which shows abrupt termination of the dye-filled veins, simulating obstruction (Fig. 11, *A* and *B*). When there is doubt on this score, the phlebogram should be repeated, using a larger amount of the contrast medium, so that the exposure of the film can be made after a longer interval of time from the start of the injection.

It is desirable to have venous pressure measurements made in conjunction with a phlebographic study. When there is obstruction in the veins of the superior vena caval system, the venous pressure usually is abnormally high and rises higher with the "exercise test." It is often found that with the development of a collateral circulation, the venous pressure becomes lower and may even become normal, although the response to the "exercise test" persists. This indicates functional improvement of the venous circulation, a fact which is not apparent from the phlebographic study alone.

**Summary and Conclusions.**—Phlebography is a simple, safe, practical method for studying obstructive lesions of the superior vena caval system. This technique, in association with comparative measurements of the venous pressure, affords unequalled precision for localization of a venous obstruction and for determination of the extent and efficiency of the venous collateral circulation.

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## ALTERATIONS IN THE FORM OF THE ELECTROCARDIOGRAM IN PATIENTS WITH MENTAL DISEASE

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IN 1940 Ljungberg<sup>8</sup> described a pattern of electrocardiographic changes occurring in a group of 90 psychotic patients. These alterations included prolongation of the P-R interval, disturbances of rhythm, notching of P waves, widening of QRS complexes, and depression of S-T segments. Meyer and Billman,<sup>16</sup> however, in an analysis of the electrocardiograms of 100 patients with anxiety states and depressions, failed to corroborate these findings. Our own experience during the routine study of tracings on patients suffering from mental disease revealed what seemed to be an increased incidence of deviations from the normal. Accordingly, the electrocardiograms from a group of 200 consecutive psychiatric patients were selected for analysis, and compared with the tracings of 200 individuals without mental disease, who were free of cardiac abnormalities.

*Material and Method of Study.* The limb leads, plus lead CF<sub>4</sub>, were taken on all of the psychiatric patients and normal subjects. In most of the patients lead CF<sub>5</sub> was also obtained. All recordings were made in the supine posture. All of the patients with mental disease and all of the subjects in the non-psychiatric group had had a physical examination and were free of objective evidence of heart disease. The observations were made in a county hospital and in an army general hospital. The 200 psychiatric patients were being routinely studied to determine their physical fitness to undergo electric shock therapy; 194 were suffering from psychosis, including schizophrenia, manic-depressive psychosis, and dementia

præcox; 4 were diagnosed as psychoneurosis with reactive depression, and 2 as having the constitutional psychopathic state. In the mentally ill group there were 182 men and 18 women. The age incidence of this group ranged from 18 to 64 years, with the majority falling in the 3rd and 4th decades. The age incidence of the non-psychiatric group varied from 17 to 60 years, with the greatest number of subjects also occurring in the 3rd and 4th decades. There were 158 men and 42 women in the control group.

**RESULTS.** The results are summarized in the table given on page 24.

**Discussion.** Forty-three psychiatric patients (21.5%) revealed 1 or more of the following aberrations of the electrocardiogram: (1) a P-R interval above 0.20 second; (2) a decrease in the amplitude of R<sub>4</sub> or R<sub>5</sub> to less than 1.5 mm.; (3) T waves of low amplitude (less than 0.5 mm.), or diphasic T waves, in lead I; (4) inverted or diphasic T<sub>4</sub> or T<sub>5</sub>; (5) the Wolff-Parkinson-White syndrome; (6) paroxysmal auricular tachycardia; (7) auricular flutter. In contrast, only 6 (3%) of the non-psychiatric patients showed 1 or more of these findings. Thus, the occurrence of these alterations was found over 7 times more frequently in the psychiatric group than in the non-psychiatric group.

As seen in Table 1, there was increased incidence (3%) of prolongation of the P-R interval in the psychiatric patients, as compared with the normal subjects. This 3% incidence is also almost double that found in a group of 1000 healthy aviators,<sup>4</sup> where only 1.6% of the subjects revealed such prolongations.

The less frequent incidence of short P-R intervals (less than 0.14 second) in the psychiatric group is noteworthy; furthermore, this frequency of such short P-R intervals in the patients with mental disease is much less than in the previously cited series of healthy aviators, in whom Graybiel *et al.*<sup>4</sup> found an incidence of 17.2% of P-R intervals below 0.14 second. The combination of an increased number of long P-R intervals, and a decreased number of short P-R intervals in the psychiatric patients suggests a vagotonic state. The influence of vagal overactivity (produced by mecholyl and prostigmin) in causing prolongation of auriculoventricular conduction time is well recognized.<sup>2</sup> Moreover, Logue, Hanson and Knight<sup>11</sup> found that in a group of 150 patients with neurocirculatory asthenia, 7 (4.6%) revealed a prolongation of the P-R interval above normal limits.

pathetic activity may produce inversion of the T waves in precordial leads and in leads II and III, as well as lowered voltage in lead I. Recently Robb<sup>17</sup> has shown that direct electrical stimulation of the cardiac sympathetic nerves may produce lowering and inversion of the T waves in dogs. That cholinergic stimuli may also produce abnormalities of T waves is suggested by the finding that inversion of T waves in precordial leads may be produced by the administration of a sympatholytic drug (ergotamine) to emotionally unstable persons without organic heart disease.<sup>19</sup>

Mainzer and Krause<sup>13</sup> have shown that fear may produce inversion of the T waves in patients about to undergo surgical operations. Loftus, Gold and Diethelm<sup>9</sup> have reported the case of a psychiatric patient in whom periods of intense anxiety were accompanied by marked lowering of

TABLE 1.—ELECTROCARDIOGRAPHIC FINDINGS IN 200 PSYCHIATRIC PATIENTS AND 200 NORMAL SUBJECTS

	No. cases in non-psychiatric group	No. cases in psychiatric group
P-R less than 0.14 second*	20	11
P-R greater than 0.20 second	1	6†
R4 or 5 less than 1.5 mm.	4	10
T1 less than 0.5 mm.*	0	11
T2 less than 0.5 mm.*	2	9
T4 or T5 inverted or diphasic*	1	16
Wolff-Parkinson-White syndrome	0	4
Auricular paroxysmal tachycardia	0	1
Paroxysmal auricular flutter	0	1

\* Exclusive of cases with Wolff-Parkinson-White syndrome.

† The P-R intervals in this group were as follows: 0.26 second (1 patient), 0.24 second (1 patient), 0.22 second (3 patients) and 0.21 second (1 patient).

The frequency of T-wave changes in the psychiatric group as compared with the subjects with normal hearts is of considerable interest. The literature reveals ample evidence that autonomic imbalance and emotional disturbances may produce abnormalities of the T waves. It has been shown that various types of adrenergic stimuli may produce lowered voltage of the T waves. The injection of adrenalin into normal subjects has been shown to produce decreased amplitude of the T waves.<sup>6,7</sup> Wendkos,<sup>19</sup> and Wendkos and Logue<sup>20</sup> have shown that increased sym-

the T waves in leads I and II. Several investigators<sup>5,11,15,19,20</sup> have shown that emotional instability and neurocirculatory asthenia may produce T-wave changes in patients free of organic heart disease. Thus, Logue *et al.*<sup>11</sup> found low voltage of the T waves in lead I, in 22 of a group of 150 patients with neurocirculatory asthenia, who were free of organic heart disease. The T waves in this latter group were also found to show aberrations in lead 2 in 21 cases.

The occurrence of a short P-R, wide QRS complex in 4 of the mental patients,

and the absence of such findings in any of the normal group would seem to be more than coincidence. The 2% incidence of this abnormality is 10 times as great as its frequency in the series of 1000 normal subjects reported by Graybiel *et al.*,<sup>4</sup> who found an incidence of only 0.2% in their series. The patient with auricular flutter is of special interest. He was found to have 2:1 block, with an auricular rate of 360 and a ventricular rate of 180. This patient was a 60 year old white male, who was admitted in a state of severe depression with suicidal tendencies. Careful physical examination failed to reveal evidence of heart disease, and the blood pressure was found to be normal. The abnormal cardiac mechanism subsided without treatment, and 2 subsequent electrocardiograms taken 3 and 12 days after the episode, were within normal limits.

The exact mechanism of production of these alterations of the electrocardiogram is obscure. However, in view of the similarity of these changes to those produced by transient emotional disturbances, as well as those caused by artificial stimulation of the sympathetic and parasympathetic systems, cited above, it would seem that both emotional instability and abnormal autonomic activity were operative in the present series of psychiatric patients. These previous observations of other investigators seem to leave little doubt that nervous influences play an important rôle in determining the form of the electrocardiogram. Severe emotional disturbances were unquestionably existent in the present group of psychiatric patients. The precise portion of the autonomic nervous system which may have been hyperactive at any moment in these patients is diffi-

cult to determine. However, the nature of the aberrations noted in the present study would seem to indicate the possibility that both adrenergic and cholinergic stimuli were operative in this group of mentally diseased patients.

The probable emotional basis of the changes observed in the psychiatric group renders it possible that in some normal individuals, similar changes might be produced by the stress of fright occurring during electrocardiographic examinations. These findings tend to expand further the broadening concepts of "normalcy" necessary for a proper appraisal of electrocardiographic changes seen in persons without heart disease. Since only 1 tracing was taken in most of the present series of patients, it could not be determined if the aberrations were permanent or transient. Their apparently benign nature, however, would indicate that caution is needed in interpreting such findings as abnormal when they are encountered in patients suffering from mental disease.

**Summary.** In a series of 200 patients with mental disease a high incidence of electrocardiographic aberrations was noted as compared with 200 normal subjects. Definite changes were noted in 21.5% of the psychiatric patients, as compared with a frequency of only 3% of such changes in the normal subjects. The similarity of many of these changes to those produced by emotional stimuli, and by artificial means of stimulation of the autonomic nervous system, is discussed. The need for caution in interpreting such findings as abnormal, when they are seen in mentally ill patients, or in normal persons who are temporarily emotionally disturbed, is pointed out.

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## CICATRIZING ENTEROCOLITIS IN A NEWBORN INFANT

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SINCE the original description of terminal ileitis by Crohn, Ginzberg and Oppenheimer<sup>6</sup> in 1932, other authors have shown that this pathologic process is not necessarily confined to the terminal ileum. Harris, Bell and Brunn<sup>10</sup> reported the occurrence of a similar enteritis in the jejunum, and Brown, Barga and Weber<sup>3</sup> as well as Crohn and Rosenak<sup>5</sup> later noted its appearance in the colon.

Regional enteritis, as it is now commonly designated, has been reported in Meckel's diverticulum,<sup>4,11</sup> and the similarity between regional enteritis and fibroplastic appendicitis has been shown by Ravdin and Rhoads.<sup>12</sup> Additional reports<sup>1,4,8</sup> indicate that the same pathologic process may involve any segment of the bowel from the duodenum<sup>9</sup> to the colon. Erskine<sup>7</sup> reported a case of acute terminal ileitis with acute appendicitis, mesenteric adenitis, salpingitis, and peritonitis in an 18 day old infant.

There appears to be no published report of the chronic form of this entity in the newborn, nor any instance in which the entire large and small bowel were involved in the pathologic process. For these reasons, it seems of interest to record the following case.

*Case History.* B. D. After an uneventful and short labor, a full-term, colored, male baby was spontaneously delivered on Dec. 8, 1945. By the 2nd day of life he had vomited repeatedly, developed abdominal distention and had passed only 1 small meconium stool. The vomitus was an odorless yellow-green liquid containing mucus. A small tube was inserted into the rectum without difficulty, and much flatus and a plug of meconium were expelled. The distention

recurred but was promptly relieved by a small colonic irrigation. A flat plate of the abdomen revealed gas in both the small and large bowel but was not abnormal. On December 15, the child was discharged having returned almost to its birth weight. Distention recurred a week after discharge but was again effectively treated with the passage of a rectal tube.

On December 28, the child, then 3 weeks of age, was readmitted because of vomiting, diarrhea and abdominal distention of 2 days duration. On admission he was thin, moderately dehydrated, and his abdomen was distended. Loops of bowel could be seen and palpated through the abdominal wall, but no masses or organs could be felt. Peristalsis was obstructive, and the character of the vomitus was identical with that of the stool. The remainder of the physical examination was essentially negative. A flat plate of the abdomen (Fig. 1) was reported as possible intestinal obstruction at the ileocecal valve. Twelve hours were spent in the administration of parenteral fluids, chemotherapy and preparation of the patient for laparotomy.

At operation, there was great distention of the small bowel proximal to the ileocecal valve. The cecum was located in its normal position in the right lower quadrant. The ileocecal valve appeared abnormal externally as though intussusception of the ileum into the cecum had begun. The terminal small bowel and the ascending colon were the site of an inflammatory process. The bowel wall was thick and the vessels engorged. As the bowel was being carefully lifted up, a small hole was accidentally torn in the friable cecum. Through this hole the ileocecal valve was explored. There was no actual intussusception. It was possible to insert a grooved director through the ileocecal valve into the terminal ileum. At this point the infant went into peripheral collapse, despite an

intravenous infusion of blood; and therefore every effort was made to get him off the operating table as soon as possible. A No. 10 rubber catheter was passed through the opening in the cecum into the terminal ileum and sutured in place to serve as a means of decompression. The abdominal contents were replaced in the peritoneal cavity only with great difficulty.

catheter into the cecum. *In situ* the small bowel appeared distended and the large bowel hypertrophic. Water could readily be introduced by syringe through the catheter into both cecum and ileum but could not be aspirated because obstruction of the fenestra by mucosal tags.

The *lungs* showed mild acute passive congestion and edema. The *liver* presented



FIG. 1.—Flat plate of the abdomen taken several hours after admission. Supine film on the left, erect film on the right.

The postoperative course was progressively down hill despite chemotherapy, the parenteral administration of fluids, plasma and blood and other supportive therapy. The abdominal distention was relieved but little by the ileostomy, and peristaltic activity was never restored. On the 3rd postoperative day the infant died.

**AUTOPSY.** (Univ. of Penna., 1946-1, 7 hours postmortem.) The body exhibited malnutrition, dehydration, scleral icterus and abdominal distention. There was a generalized fibrinous peritonitis and a droplet of pus was uncovered about the entrance of the

fatty dystrophy and some of its canaliculi were filled with bile pigment casts. The *kidneys* showed a few scattered convoluted tubules in which the epithelium was replaced by calcium deposits.

The lesions of interest were in the intestinal tract. The *esophagus* and *stomach* were normal. The serosa of the intestines was covered in places with fibrinous exudate, and exhibited dark green discolored patches. The entire small bowel was dilated. The wall of the proximal *small bowel* was thickened but friable throughout. The thickening increased from the duodenum distally

and was maximal at the ileocecal valve, appendix, cecum and ascending colon but then lessened gradually toward the anus. In the colon the thickening involved the submucosa, muscularis, and the tissue external to the muscular coat (Fig. 2). The mucosa of the distal two-thirds of the ileum appeared gray-brown and friable; it peeled off easily and was absent in thin transverse patches. The mucosa of the *colon* from the ileocecal valve to the anus had a thickened cobblestone appearance. In the sigmoid there was a small, round, punched-out ulcer about 3 mm. in diameter with a ragged base. There was a no point of frank obstruction.

cells the nucleus was eccentric. Lymphatics often contained exudate. In addition, there was necrosis of the mucosa and part of the submucosa, with a mild superimposed polymorphonuclear response.

The colon exhibited a most pronounced picture of chronic inflammation, fibrosis and hypertrophy of the muscular coats (Fig. 4). The mucosa was thrown into high thick folds and fibrosis was marked in the submucosa and the tissue external to the muscularis. The histologic appearance varied considerably from place to place. The mononuclear exudate was more marked in some places than in others while fibrosis

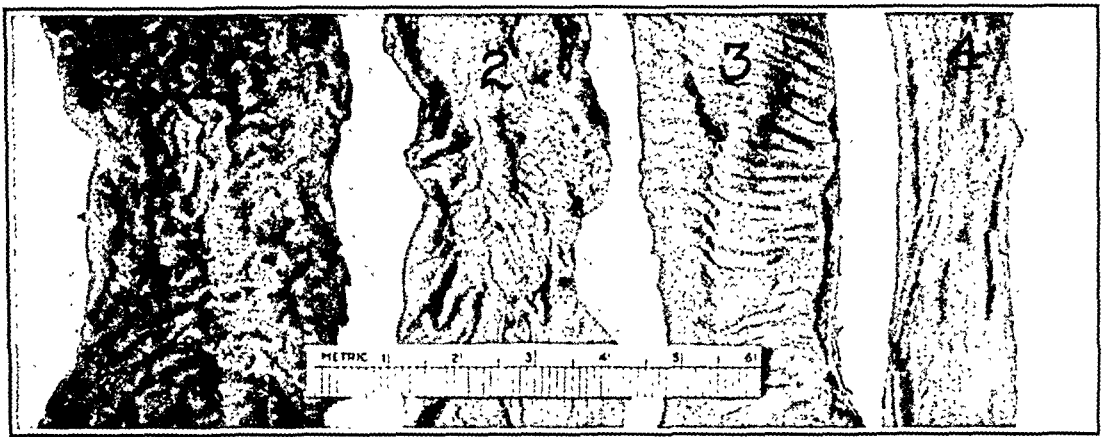


FIG. 2.—Bowel of 3 weeks old B. D. compared with normal bowel of 6 weeks old infant. 1, Colon of B. D.; 2, normal colon; 3, ileum of B. D.; 4, normal ileum.

On section, the wall was thickened not only in its submucosa but also in its musculature, including the muscularis mucosæ. This was evident by comparison of similar sections of small and large bowel of a normal 6 weeks old infant (Fig. 3). The thickening, however, was due more to the inflammatory changes in the submucosa and subserosa than to hypertrophy of the muscularis.

*Microscopic examination* of the proximal ileum showed some autolysis but, nevertheless, it was obvious that the wall was thickened. The musculature was hypertrophic; the submucosa and subserosa were thickened by fibrosis, hypermia, edema, and an exudate of cells which were difficult to recognize because of the autolysis. The distal ileum showed similar changes, but they were more marked. The exudate was composed of mononuclear leukocytes, small and large; they were characterized by round, dense nuclei and varying amounts of cytoplasm which was sometimes basophilic. In some

was prominent elsewhere. Often fibroblasts and new vessel formation were apparent. There were no giant cells. There were occasional eosinophils and often macrophages with finely vacuolated cytoplasm. Occasionally there was fibrinoid degeneration of collagen. Some arteries had thickened dense adventitia. Occasional small vessels contained platelet thrombi enmeshing red cells and leukocytes. The appendix showed similar changes.

A section of the sigmoid ulcer showed a defect which involved the mucosa, submucosa, and part of the muscularis and which undermined the mucosal edges. The base was necrotic and the submucosa along the edges was greatly thickened by the same changes described above, but eosinophilic leukocytes occurred frequently. In the rest of the section the changes were much less evident than those higher in the colon.

The mesentery was greatly thickened, and the lymph nodes were enlarged, soft, discrete

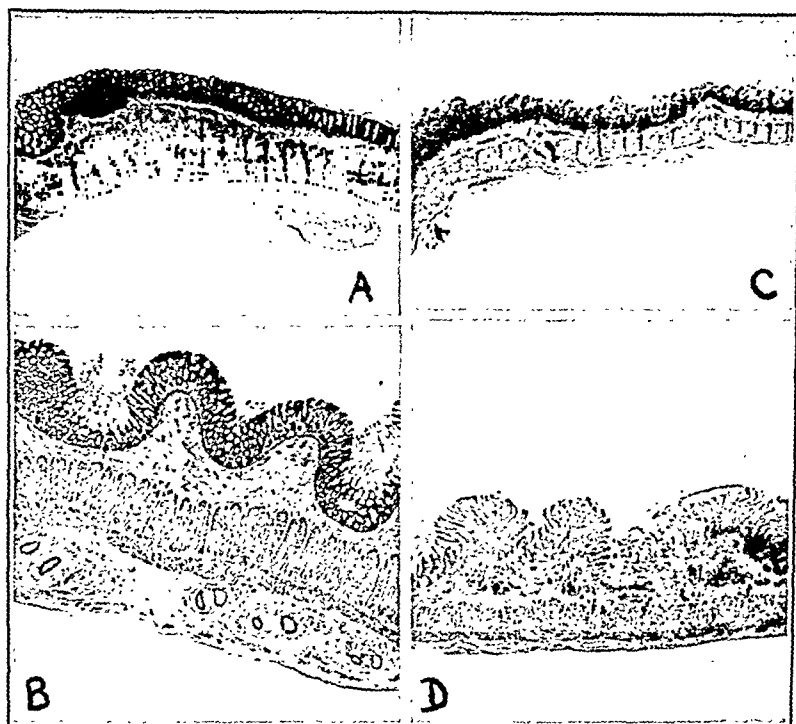


FIG. 3.—Photomicrographs of sections of bowel; B. D. compared with normal. A, Normal colon; B, enlarged colon of B. D.; C, normal ileum; D, enlarged ileum of B. D.  $\times 10$ .

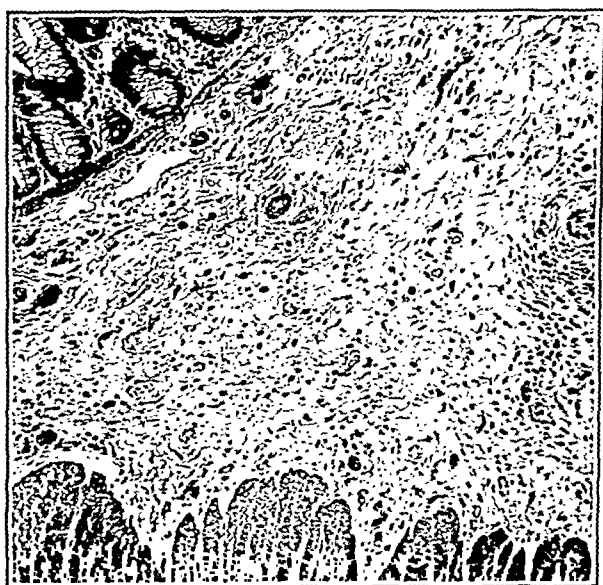


FIG. 4.—Case B. D. Photomicrograph of submucosa of colon. Note marked fibrosis and mononuclear exudate.  $\times 73$ .

and pale gray in color. The mesenteric serosa showed an acute fibrinous inflammation, part of the generalized peritonitis. The chronic inflammation seen in the wall of the bowel was also present in the mesentery (Fig. 5) but, in addition, there were foci of polymorphonuclear cells scattered about. The arteries showed marked dense adventitial thickening (as if it were part of the general fibrosis), and the elastic laminae were thrown into deep folds. The lumens appeared relatively small. Similar but milder changes were seen in the connective tissue about the pancreas.

**Comment.** As the infant died when less than a month old, it would seem from the chronic nature of the process (chronic inflammation, fibrosis and hypertrophy of the bowel) that it had begun *in utero*. The fact that symptoms and signs were present from birth may well support this assumption.

Physical examination and barium study of the mother's gastro-intestinal tract re-



FIG. 5.—Case B. D. Thickened mesentery. Left: illustrates thickened narrowed mesenteric vessels.  $\times 8$ . Right: shows fibrosis and mononuclear exudate, with portion of lymph node at extreme right.  $\times 73$ .

The *lymph nodes* were depleted of lymphocytes. The sinusoids contained numerous small and large mononuclears and sometimes neutrophils, although the nuclei tended to be pyknotic so that the cells were difficult to classify. The macrophages in both the nodes and the mesenteric connective tissue often had a fine pale vacuolization in their cytoplasm.

Loeffler stains revealed no bacteria in bowel, mesentery, or mesenteric nodes. Cultures were not taken. Fat stains showed no fat in the macrophages of bowel or mesentery.

vealed no demonstrable lesion other than a cystocele. She had been in good health throughout her entire pregnancy and was Rh positive.

**Summary.** A unique case of chronic enterocolitis involving the entire small and large bowel in a newborn is reported. It seems likely that this lesion had its origin in prenatal life.

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# THE NEUROMUSCULAR SYSTEM IN RHEUMATOID ARTHRITIS

## ELECTROMYOGRAPHIC AND HISTOLOGIC OBSERVATIONS\*†

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MUSCLE weakness, usually associated with atrophy, constitutes one of the most disabling features of rheumatoid arthritis. If the muscle atrophy becomes established, it undoubtedly contributes to joint deformity and presents a major hindrance to the regaining of the normal joint function. In addition, early in the disease, motor weakness, often accompanied by numbness and paresthesias, may strongly suggest the diagnosis of a primary neurologic disorder. The problem of muscular atrophy in arthritis has attracted the attention of numerous clinical observers and has led to animal experimentation in an attempt to elucidate its origin. Since rheumatoid arthritis cannot be reproduced in animals, the present investigation is entirely upon the human subject and utilizes both electromyographic tracings and histologic studies of the central nervous system, the peripheral nerves and the voluntary muscles.

**Electromyographic Observations.** The observations which were made with the

aid of electromyographic tracings were divided into several parts. The first comprised the recording of voluntary contractions, which were compared with those obtained from normal individuals. In the second part, the object was to ascertain whether or not involuntary activity was present, such as is seen, for example, in progressive muscular atrophy in the form of fasciculations.‡ Finally since the increased reflexes and even clonus<sup>34,38</sup> often found in rheumatoid arthritis suggest spasticity, we looked for the 2 outstanding electromyographic characteristics of this state, which have recently been pointed out by Hoefer and Putnam.<sup>29</sup> These are synchronization in pattern and frequencies of motor unit records when 2 or more coaxial electrodes are inserted into a muscle during a gentle voluntary contraction and a spread of tendon reflexes to muscles served by reflex arcs at other levels or even on the opposite side of the body. We may anticipate the description of our results by stating here

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‡ Throughout this paper, the commonly understood distinction between fasciculations and fibrillations will be adhered to. The former, which are visible through the skin, are considered to be contractions of groups of muscle fibers making up single motor units. Fibrillations, on the other hand, which can be seen only through mucous membrane or on the surface of an exposed muscle, represent contractions of single muscle fibers and arise consequent to denervation. Another possibility suggested by recent observations<sup>16,27</sup> should be mentioned, that synchronized fibrillations may result in "fasciculations."



that tracings from voluntary and reflex muscle contractions in patients with rheumatoid arthritis showed no apparent deviation from the normal and gave no hint of spasticity. We did find involuntary muscular activity, however, which we attempted to define by comparison with that recorded in recognized neuromuscular disorders and to delimit its point of origin by procaine block of the common peroneal nerves.

**Material and Methods.** The largest group of patients tested comprised those with well-marked rheumatoid arthritis, 34 in number. These were all being treated on the hospital wards and were therefore, with 1 exception, of moderate or marked severity. There were 16 males and 18 females, with ages ranging from 12 to 58, with a mean of 35.6. The duration of the disease varied from 6 months to 13 years, with a mean of 5.2 years. Six of the patients, all males, had involvement of the spine in addition to peripheral joints. No form of selection was used and the patients represented a cross-section of the disease as seen in hospital practice. As a corollary to the study of the patients with rheumatoid arthritis, an additional group of patients with articular, muscular, or neurologic disease was tested for involuntary muscular activity. These comprised 3 patients with acute gonorrheal arthritis, 1 patient with acute specific infectious arthritis of unknown etiology, 2 patients with Charcot joints secondary to tabes dorsalis, 1 patient with joint disability following fixation, 1 patient with dermatomyositis and 2 patients with progressive muscular atrophy. As a final check, the muscles of 10 normal controls were tested for evidence of spontaneous activity.

The muscles chosen for examination were those in relationship to involved joints and included in the upper extremity, the triceps, biceps and the flexor and extensor muscles of the forearm. In the leg, the quadriceps, hamstring group, anterior tibial and gastrocnemius were most commonly tested. The results obtained from each were similar and did not vary in respect to the muscle chosen. In the normal controls, we searched for involuntary activity in all of the arm and leg muscles listed above.

Both surface and needle electrodes were used to obtain the action potentials from

the muscles. The former were flat solde disks, 6 to 10 mm. in diameter and attached to No. 32 enamelled copper wire. The skin above the muscles to be studied was cleansed with acetone, Sanborn electrocardiograph paste was applied and the electrodes were kept in place with adhesive tape. Two such electrodes constituted a bi-polar lead and were placed 3 to 4 cm. apart along the axis of the muscle. The usual resistance in such a placement was 5000 to 10,000 ohms. Contraction of the muscle under the skin did not displace the electrodes and other source of artefact such as motion in the electrode wires were carefully avoided. The needle electrodes were usually made of an insulated copper wire held in place within a hypodermic needle. The exposed end of the copper wire formed 1 electrode and the needle itself the other. Another method was to insert into the muscle a needle large enough to permit the passage of 2 30-gauge wire free from insulation only at the tips, which were kept slightly separated. With the wires in place within the muscle, the needle was withdrawn, leaving a bi-polar electrode consisting of 2 wires rather than a wire within a needle. The gain on the amplifiers was set so that in the relaxed normal muscle no deflection of the pens occurred. This represented a 1 cm. deflection for 100 microvolts of input during inactivity and for 300 microvolts during voluntary contractions.

Amplification and recording of the muscle action currents were obtained by 2 types of ink-writing oscillographs, with both giving similar results. One was a Grass 3 channel instrument with paper speeds varying from 1.5 to 6 cm. per second. With the second, designed and built by Loomis,<sup>37</sup> recordings could be made simultaneously in 6 channels at a paper speed of 3 cm. a second. The characteristics of both of these amplifiers are identical in that they have the first 2 or 3 stages entirely dependent on battery sources of power before feeding the power amplifiers run from commercial 60 cycle current. Both are linear up to several thousand cycles and have time constants of  $\frac{1}{2}$  second. Both are condenser coupled with push-pull circuits and especially suited for the operation of the moving coil type of ink-writing oscillographs used in recording alternation potentials from 1 to 70 cycles.

The limitations of this method of recording for electromyography have been a source

of controversy, as it fails to record the wave form above 70 cycles and registers only a fraction of the potential of fibrillary spikes which last 1 to 3 milli-seconds. On the other hand, the advantage of being able to record continuously from several muscles with immediate availability of the record can only be obtained with ink-writing oscillographs. Records of film exposed to the cathode ray, which records all of the fast frequencies up to many thousand cycles, give a picture free of the disadvantages described above; but such records are not visible until the film has been developed and multiple recording is both difficult and expensive. Changes in the electromyogram that occur rapidly, even from second to second, in response to alteration in posture or the development of tension or relaxation show up most clearly in the multichannel ink-writer type of recorder. What is lost is fidelity of pattern or from frequency limitation is offset by the immediate availability of the record for inspection and study. A combination of both types is ideal and future observations will include both cathoderay inspection and photographs.

Attempts were made to keep the patients as comfortable and relaxed as possible while tracings were being made. Otherwise the results were confused by a varying amount of muscular tension which could be electrically recorded in both arthritic and control subjects. We have also shared the experience of Jacobson<sup>33</sup> that some individuals are difficult or even impossible to relax. Such patients, who made up a very small minority, were discarded from either the arthritic or control groups. Painful and deformed joints were supported in the position of maximum comfort. During the recording the patients were supine or lying on one side, but, while the patellar reflexes were elicited, they were seated with feet supported.

Blocking of the common peroneal nerve was obtained with the infiltration of 2% procaine into the region where the nerve passes across the fibula just below its head. In each case, the block was proven complete and successful by the absence of electrical activity over the anterior tibial muscle when voluntary dorsiflexion of the foot was attempted. In addition, vasomotor and sensory paralysis was evident in the distribution of this nerve.

**Results.** Voluntary contractions were electrically recorded from the extensor and flexor muscles of the forearm while the patient squeezed a rubber bulb. The amount of air expelled from the bulb was recorded on a moving drum by means of a basal metabolism machine. In this way, a rough measurement of the patients' strength (ergogram) could be obtained simultaneously with the electromyograms of the muscles concerned. No consistent deviation was obtained from the recordings of normal controls. At times the electromyographic tracings exhibited an amplitude which was comparable to that obtained from normal individuals, but at times it was decidedly lower. In general, the patients with rheumatoid arthritis tended to relax less readily between squeezes, and the ergographic tracings demonstrated what was apparently marked weakness and rapid fatigability. Both of these findings, however, could be accounted for on the basis of painful and limited finger joints, as well as on muscular weakness or spasm. Tracings from voluntary contractions of other muscles which were associated with arthritic joints of both the leg and arm grossly resembled those from persons without articular disease.

We have mentioned that we were not able to demonstrate either of the 2 outstanding characteristics of spasticity: synchronization of motor unit leads or a spread of tendon reflexes.<sup>29</sup> Two coaxial needle electrodes were inserted into either the quadriceps or triceps muscles of 8 patients with rheumatoid arthritis and repeated gentle voluntary contractions elicited. In every instance, the complete independence of motor unit leads was apparent, a feature which has been well illustrated by Hofer and Putnam as characteristic of normal individuals without spasticity<sup>29</sup> or rigidity.<sup>30</sup> In 10 patients with rheumatoid arthritis, patellar reflexes were obtained while surface electrodes were placed over the opposite quadriceps and over the forearm muscles. An apparent spread of reflexes was noted

at first, but this was proven to be due to a movement artefact<sup>47</sup> and could be produced in normal individuals. By more careful adjustments of the patient's position and of the recording wires, these artefacts could be eliminated. After such precautions had been taken, although elicitation of the patellar jerks in several of our patients produced such a violent response that the whole body shook, no evidence of a spread could be picked up through the electromyogram.

Next, with the idea that the muscle weakness and atrophy of rheumatoid arthritis might somehow be concerned with involuntary activity rather than disuse,<sup>24</sup> we applied surface electrodes over the muscles of such patients when they were immobile and apparently comfortable and relaxed. In many of them we picked up action currents as shown in Figure 1, 1 and 2. These tracings are from 2 different patients and represent variations in the rate and amplitude of these regular diphasic spikes. In the first tracing, the rate is 15 to 20 per second, and in the second, 6 per second with amplitudes of 40 and 25 microvolts respectively. We found this pattern in tracings of the muscles obtained with both surface and needle electrodes in 50% (17 out of 34) of the rheumatoid arthritics tested. There was no apparent relationship between the presence or absence of this activity and the age, sex, duration or severity of disease, involvement of the spine or the degree of visible muscular wasting. While such tracings were being recorded, no evidence of muscle activity was apparent to patient or observer. This activity

usually appeared and disappeared spontaneously as shown in Figure 1, 2 and 3. In some patients, it lasted only a few minutes; in 1 we were able to follow it for an hour without change or let-up. In 4, the disappearance of the activity was obtained by making the patient more comfortable by putting a pillow under a pair of inflamed knees. In 5, it reappeared again, with the removal of the pillow. In others, however, it persisted in spite of every attempt to increase the comfort and relaxation of the patient. The elicitation of a reflex contraction of the muscle concerned had no effect, either in initiating the pattern, nor, while present, causing its disappearance. Occasionally, the series of regular spikes could be brought out by a voluntary contraction, as in 6, where one may see a series of voluntary contractions followed by spontaneous activity. Occasionally, they could be abolished by a voluntary contraction, as in 7, but in general, as shown in 8, the pattern persisted, no matter how often interrupted by voluntary contractions.

Another characteristic was that the activity might be found at a given time over only one localized area in a large muscle like the quadriceps, when 6 channels were used to record electrical impulses from variously located surface electrodes. On several occasions spontaneous activity was present in 1 muscle related to a joint and not in another. Thus, in respect to a knee joint involved in rheumatoid arthritis, regular diphasic spikes might be obtained from the quadriceps and not simultaneously from the hamstrings, with the reverse true at a later

#### LEGEND FOR FIG. 1.

Fig. 1.—Involuntary skeletal muscle activity in patients with rheumatoid arthritis, showing influence of discomfort and of voluntary contractions. Surface electrodes. Time recorded at top in seconds. 1, Regular diphasic spikes obtained from skeletal muscle apparently at rest of patient with rheumatoid arthritis. Rate 15 to 20 per second; amplitude 40 microvolts. 2, Same as 1. Rate 6 per second, amplitude 25 microvolts. Spontaneous cessation of activity. 3, Same as 1 and 2. Spontaneous disappearance and reappearance of activity. 4, Disappearance of activity in quadriceps muscle of patient with rheumatoid arthritis of knees when pillow placed under them. 5, Reappearance of activity in same muscle when pillow removed. 6, Regular diphasic spikes apparently brought out by voluntary contraction of quadriceps of patient with rheumatoid arthritis. 7, Activity apparently abolished in same muscle by voluntary contraction. 8, Persistence of activity in same muscle in face of repeated voluntary contractions.

examination. However, we found no constant relationship of flexor activity with resultant reciprocal extensor inhibition, as has been postulated in explanation of the more common extensor atrophy seen in rheumatoid arthritis.<sup>19</sup> One very interest-

ing finding in a patient with unilateral arthritis was the occurrence of this pattern in the forearm muscles of the as yet uninvolved and asymptomatic side (Fig. 2, 1). The following week she developed pain and early arthritic involvement of this

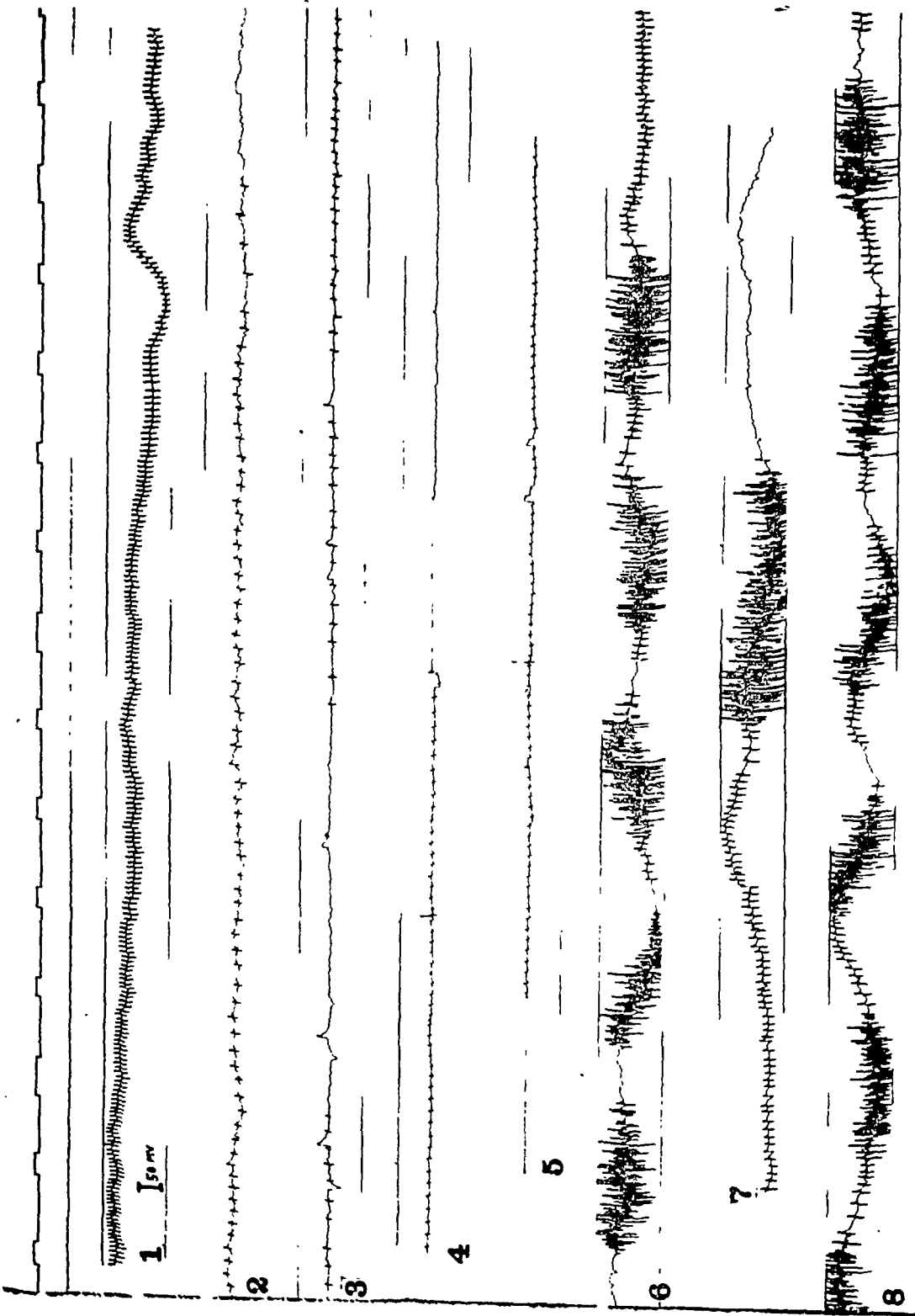


FIG. 1

hand. In this patient, then, disturbed muscle function apparently preceded any clinical evidence of articular disease, an observation which bears out the similar clinical findings of Jones.<sup>34</sup>

Is this spontaneous muscular activity

peculiar to rheumatoid arthritis? An example of this same pattern obtained from 2 out of 4 patients with acute specific infectious arthritis (3 gonorrheal and 1 of unknown origin) is shown in Figure 2, 2. Below, in 3, we may see the same regular

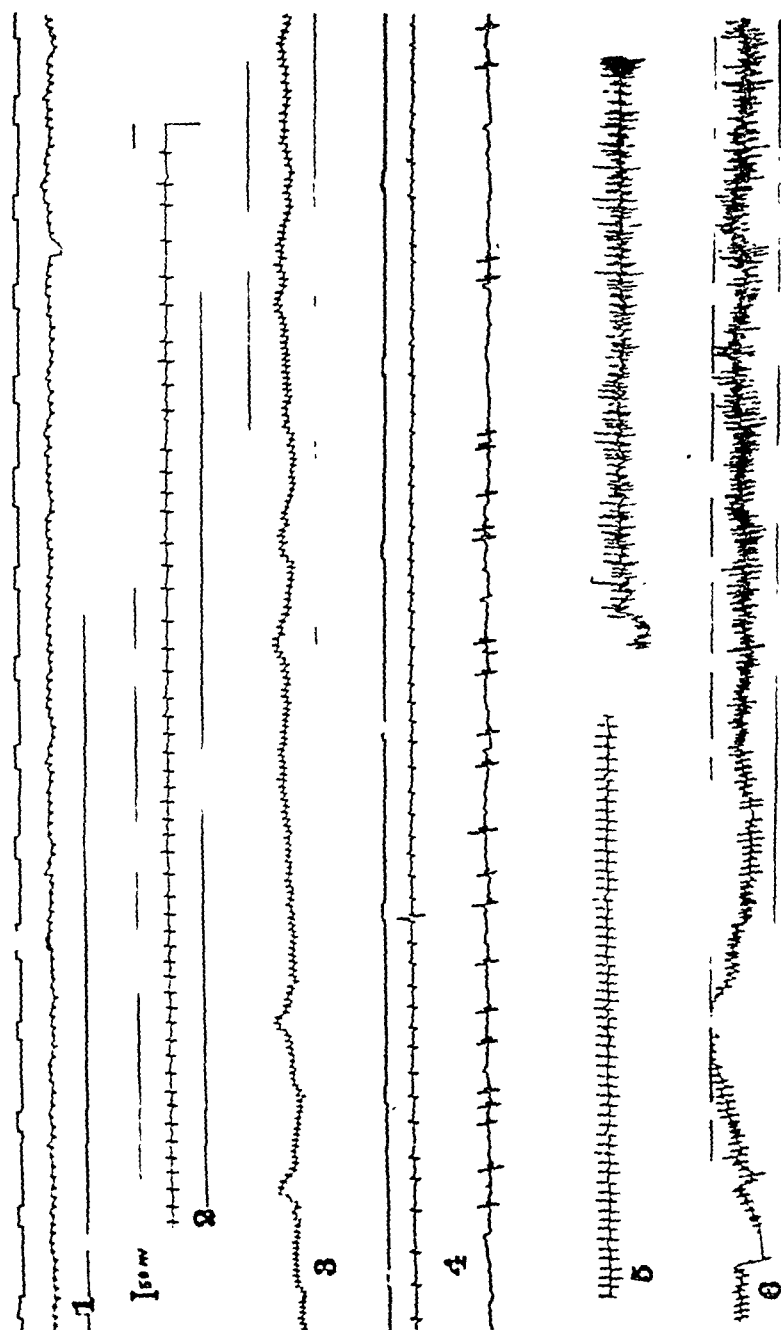


FIG. 2.—Electromyographic tracings of involuntary skeletal muscle activity in rheumatoid arthritis, gonorrheal arthritis, joint fixation and progressive muscular atrophy. Time at top in seconds. 1, Involuntary activity in the extensor muscles of the forearm, with the related joints as yet uninvolved and asymptomatic. Patient had rheumatoid arthritis of the joints of the opposite arm. Surface electrodes. 2, Regular diphasic spikes obtained from the biceps of a patient with acute gonorrheal arthritis of the elbow. Surface electrodes. 3, Similar pattern, recorded from the triceps of a patient with shoulder joint disability due to fixation. Surface electrodes. 4, Two examples of fasciculations recorded from the muscle of a patient with progressive muscular atrophy. Surface electrodes. 5, Recording of a weak voluntary contraction in a normal subject with needle electrodes. (Time directly above in seconds for this tracing only.) 6, Recording of a weak voluntary contraction in a normal subject with needle electrodes. The second half shows the result of increased effort—the usual complex pattern of a voluntary contraction. 6, Regular diphasic spikes from a resting skeletal muscle of a patient with rheumatoid arthritis merging into a complex pattern as in 5. Surface electrodes.

series of spikes obtained from the triceps of a patient without any arthritis. This young man had had a lobectomy for bronchiectasis. As part of the postoperative management, his right arm was strapped to his side for 3 weeks and had just been freed. He still had pain on full abduction and rotation of the shoulder. Thus, with the same patterns found in specific infectious arthritis and in joint disability due to fixation, one cannot assign this phenomenon exclusively to the muscles of patients with rheumatoid arthritis. However, in examining the limb muscles of 10 normal controls in an attempt to find activity of this nature, only a few isolated groups of diphasic spikes were observed, nor was involuntary activity present in the muscles of 2 patients with Charcot joints and 1 with dermatomyositis.

Recent observations have shown a closely similar pattern of involuntary discharges to be present in a number of diseases or injuries of the central or peripheral nervous system. In anterior poliomyelitis, spontaneous discharges are a striking feature, especially in the convalescent stage, when they are a sign or improvement in muscle function.<sup>5,60</sup> The same is true of nerve injuries<sup>48,59,61</sup> and infectious polyneuritis<sup>5</sup> with the electromyographic tracings in the 3 conditions resembling each other as well as those we have described in rheumatoid arthritis. The electromyogram is also useful in localizing impairment of muscle innervation from spinal cord lesions, both neoplasms and ruptured intervertebral disks<sup>11,31,59</sup> by means of the recording of involuntary activity in the muscles concerned, with the pattern again resembling that found in rheumatoid arthritis.

The point of origin of the nerve impulses which bring about the spontaneous muscular activity in the diseases or injuries of the nervous system mentioned in the preceding paragraph has not been defined. From the location of the primary pathologic process, it may be assumed to originate in the case of anterior poliomyelitis

from anterior horn or internuncial cells and in nerve injuries and infectious polyneuritis from peripheral nerve fibers. When spinal tumors and ruptured intervertebral disks are concerned, however, the activity may be a response to stimuli anywhere along the lower motor neurone or indeed, as pointed out by Hoefer and Guttman,<sup>31</sup> through sensory pathways or from intramedullary structures some distance away from both sensory and motor roots. The application of these concepts furnishes little assistance in the localization of the origin of the involuntary motor activity found in rheumatoid arthritis. The observations outlined in the next paragraph were therefore made, in an attempt to determine to some extent the source of the nerve impulses responsible for this activity.

In 8 patients with rheumatoid arthritis involving the ankle and, or, knee joint, a successful block of the motor and sensory fibers of the common peroneal nerve was performed with 2% procaine. In none of the patients was spontaneous activity present in the anterior tibial muscle following the procaine block, although continuous electromyographic recording was performed for at least 15 minutes. In 5 of the 8, the characteristic pattern which we have described was present before the nerve block. Tracings were also made from the opposite anterior tibial muscle, the nerve supply of which was not interrupted. In 1 patient, activity was present in this muscle both before and after the nerve block. Due to the inconstant nature of these series of diphasic spikes, which, as we have shown, appear and disappear spontaneously, it is difficult to draw conclusions from acute experiments of this nature. However, since the results were so constant in these 8 cases, there seems little reason to doubt that blockage of the peripheral nerve is capable of interrupting the path of origin of these motor discharges. We can thus at least place their source proximal to the point of blockage, but more definite

localization must await further experimentation.

Spontaneous motor activity is found also in other disorders of the neuromuscular system, but in each case the pattern is different from that encountered in rheumatoid arthritis. Fibrillations, which follow denervation of a muscle by section of its motor nerve, can be distinguished from the diphasic spikes which appear with beginning return of function and which, as we have stated, resemble the involuntary activity in rheumatoid arthritis. Both types of activity may sometimes be present at a certain point in the recovery process following nerve injuries.<sup>61</sup> Whether or not such may be the case in rheumatoid arthritis cannot be determined from our observations, since fibrillations are difficult to demonstrate with the ink-writing oscillographs used. The pattern of the muscular activity caused by tetanus toxin<sup>26,58</sup> is also unlike that observed in rheumatoid arthritis, while rigidity associated with extrapyramidal lesions is characterized by irregular electromyographic activity resembling that of a sustained voluntary contraction, although of about one-fourth the average amplitude.<sup>30</sup> Finally, the "rest activity" seen in a certain type of myositis<sup>6</sup> is also similar to the tracing of a moderate voluntary contraction. Thus, the spontaneous muscle activity of rheumatoid arthritis, while resembling closely that found in 4 types of neuromuscular disorders, is unlike that described in the last 4 forms.

The electromyographic pattern of the fasciculations characteristic of progressive muscular atrophy may superficially resemble that of rheumatoid arthritis, as shown by the upper line of Figure 2, 4. The lower line of this tracing shows a more characteristic run of fasciculations with a more easily recognizable dissimilarity. Another difference lies in the fact that fasciculations may be brought out or intensified by the injection of prostigmine,<sup>15</sup> which was not the case in respect to the spontaneous muscular activity of patients with rheumatoid arthritis. It

has been postulated<sup>60</sup> that the differing patterns found in progressive muscular atrophy and in nerve injuries, infectious polyneuritis and anterior poliomyelitis may depend upon the progressive degeneration taking place in the former contrasted to regeneration in the latter 3 conditions. It is of some interest in this respect that tracings recently taken from a patient with rheumatoid arthritis who developed paralysis of dorsiflexion of the foot resembled to a large extent the fasciculations of progressive muscular atrophy. The evidence is conflicting as to the usual point of origin of the fasciculations of progressive muscular atrophy. Experiments utilizing nerve blocking<sup>22,46,50</sup> or interruption<sup>16</sup> have tended to place the origin of the involuntary activity in the distal portion of the nerve, in contrast to our findings in rheumatoid arthritis. It is probable, however, that they may arise at times from any portion of the lower motor neurone, from the cell body to the myoneural junction.<sup>54</sup>

As stated above, sustained involuntary activity was not observed in control patients without arthritis. However, with a concentric needle electrode, which is small enough to pick up the action currents of a single motor unit, it is possible for a normal subject, with a very gentle muscular contraction, to produce a series of spikes as shown in Figure 2, 5. These may persist, at 9 or 10 to a second, for nearly a minute. With increased effort, the pattern becomes that of a voluntary muscle contraction, as shown in the adjacent tracing. Similarly, the regular series of diphasic spikes from the muscles of an arthritic may merge into a complex pattern indistinguishable from a voluntary muscle contraction (Fig. 2, 6). This may persist for several minutes without the patient himself being aware of it.

Others have noted<sup>1,21,49</sup> these single-spike discharges of constant height and form recorded in weak voluntary contractions by means of needle electrodes. From their morphology, they have been regarded as recordings of the contractions of a

single motor unit (a group of muscle fibers innervated by a single motor nerve fiber), but of course may represent simultaneous contractions of more than 1 motor unit. With a stronger contraction, more motor units in the vicinity become active and a complex pattern is obtained, in which it is impossible to distinguish the single motor units. In patients with nerve injuries, however, with consequent reduction of a number of active nerve or muscle fibers, a single motor unit pattern of response may be obtained even with maximum efforts.<sup>9,49,51</sup> The tracings from both of these responses resemble quite closely the involuntary muscular activity in patients with rheumatoid arthritis. It seems reasonable then to assume that in this disease there is often only a single motor unit at work in a given area, a situation which the regular series of spikes probably represents. A similar conclusion has been drawn by those who have observed a like pattern of spontaneous activity in anterior poliomyelitis, infectious polyneuritis, nerve injuries and spinal cord lesions.<sup>5,11,31,59,60,61</sup> The reason for this is not clear at present, but 2 possibilities arise by analogy with the recordings of voluntary contractions. The first is that the activity is of a slight degree and utilizes only a single motor unit in a given area, the second that through muscle atrophy the number of active muscle fibers has been reduced in the vicinity of the recording electrode. At present, at least in the case of rheumatoid arthritis, the first possibility seems more plausible, since a full voluntary muscle contraction was possible in all the individuals studied, and since, as we have demonstrated, the single motor unit activity not uncommonly merged into the pattern of a fairly strong muscular contraction. Of course, a combination of the 2 may be at work.

**Histologic Observations.\*** We have had the opportunity of examining, postmortem, the central nervous system in 44 patients with rheumatoid arthritis. Since

certain degenerative changes of the parenchymatous tissue and proliferative changes of the interstitial tissue are regularly found associated with advancing age alone, a careful comparison was made with a control group of 50 cases of similar age distribution but without rheumatoid arthritis. No specific lesions were found in the brain or spinal cord in the cases with rheumatoid arthritis, but alterations usually attributed to aging were more pronounced than in the controls. The histologic alterations in both arthritics and controls included degeneration and diminution in number of anterior horn cells, loss of axons and their myelin sheath in various regions of both white and gray matter, and a concomitant gliosis replacing this loss of parenchymatous tissue. As far as could be ascertained, no lesion of the upper motor neurones was present, a finding in accordance with the electromyographic observations.

The anterior horn cell changes consisted largely of 3 types of degeneration. *Chronic shrinkage* in which the cell body was reduced in size, the nucleus pyknotic, the tigroid substance clumped and hyperchromatic and in which the cell was accompanied by few, if any, satellites, was the most common nerve cell alteration. *Pigmentary atrophy* was next most frequently found and this disease was characterized by increase in lipofuchsin with a loss of Nissl substance. Sometimes the cell was apparently increased in size with an eccentric nucleus, and the cell membrane, bulging outward, was filled with bright yellow pigment in the Nissl stain, while only a very few tigroid bodies remained. Such a cell was often accompanied by a ring of satellites, chiefly oligodendroglia, and neuronophagia was sometimes encountered. A very common finding was glia nodules, small scars of glia presumably marking the sites of former nerve cells. These 2 types of anterior horn cell disease are usually regarded as primary degenerations. They were found

\* One of the authors, Dr. L. R. Morrison, will report in detail elsewhere on the histologic examination of the neuromuscular system in rheumatoid arthritis.



in the mesial cell groups that control the musculature of the trunk, and more particularly in the lateral groups wherein are located the cell bodies of the nerves that innervate the muscles of the limbs. A third type of cell disease, *retrograde degeneration*, was found principally in the lateral projections of the anterior horns and only in the arthritic group. This lesion consisted of swelling of the cell body, central chromatolysis with peripheral pyknosis, occasionally vacuolation, and, very often, eccentricity of the nucleus. Examples of this "axonal reaction" were found in one-fourth of the 44 cases.

Anterior horn cell changes in rheumatoid arthritis have been described by previous workers, although in no instance has comparison been made with a control group. The earliest report encountered is that of Folli<sup>18</sup> in 1893, followed by Bannatyne<sup>3</sup> in 1898, Mott and Tredgold<sup>39</sup> in 1902 and by Penny<sup>41</sup> in 1913, who made careful and detailed observations on anterior horn cell alterations in 6 cases.

Changes were also observed in our patients in the white matter, including loss of myelin, disease and disappearance of axons and hyperplasia of astrocytes, but they were not greater than could be ascribed to advancing age. The same can be said of the alterations in Clarke's column, in contrast to the anterior horn cell degeneration, which, while not specific, was definitely more advanced than in the control group.

In the peripheral nerves, lesions were found somewhat similar to those described by other investigators.<sup>3,12,17,18,20,29,41,45,53</sup> In 26 out of 31 cases, inflammatory reactions were present in the nerve sheath, chiefly in the perineurium. The reaction consisted largely of lymphocytes and plasma cells with endothelial and occasional epithelioid cells or monocytes present as well. Sometimes, as emphasized in recent reports,<sup>17,18,23</sup> these foci were nodular in appearance (Figs. 3 and 4), and had an indefinite, acellular center, at times resembling collagen. The eosinophilic central region did not show fibrinoid degen-

eration, however, and neither was there any conspicuous reaction of epithelioid cells. A fairly dense zone of lymphocytes would often surround the acellular center while plasma cells and monocytes were more apt to be found at the periphery. There was no fibroblastic capsule surrounding the outer layer but a fairly sharp line of demarcation was brought about by the interstitial tissue of the nerve, either the perineurium, or, less commonly, the epineurium. More frequently, however, the zones were less clear-cut and the lesions looked less nodular, being sometimes long and narrow with lymphocytes and plasma cells more or less intermingled and the inflammatory reaction often situated in relation to a blood-vessel. In addition to these paravascular collections of reacting cells, there were occasionally other groups, chiefly lymphocytes, found in relation to the endoneurium, too small to have any definite shape yet conspicuous enough to be called pathologic and not found in normal nerves.

While these lesions were not ordinarily in direct relation to the parenchymatous structures, the various nerve sheaths being interposed, the myelin sheaths and the axons often showed pathologic changes. These changes, while distinct enough, were of a scattered, isolated distribution without widespread patches of nerve degeneration. Usually the axons and medullary sheaths were affected individually or in small groups, commensurate with the small size and number of the perineuritic foci. Silver impregnations were not done on some of the cases, but on those on which they were done 16 of them showed alterations of the axons ranging from thickening through moniliform swellings up to vacuolation, fragmentation and tortuosity (see Figs. 5 and 6).

Alterations in the myelin sheath, while not extensive nor always present, were seen in the Oil Red O and the Weigert or Weil stains. They also varied in degree from slight thickening and pallor to complete myelin breakdown, with myelin figure formation, gutter cell activity and

frank patches of demyelination (Fig. 7). This disease of the myelin was evidently of a progressive nature, for in some cases of long standing, severe arthritis, there was increased connective tissue stroma in the nerve preparations, yet at the same

time fat-laden phagocytic cells were still active.

On account of the disease of the axons of the peripheral nerves, there were certain axonal reactions, or retrograde degenerations, in the corresponding nerve cell

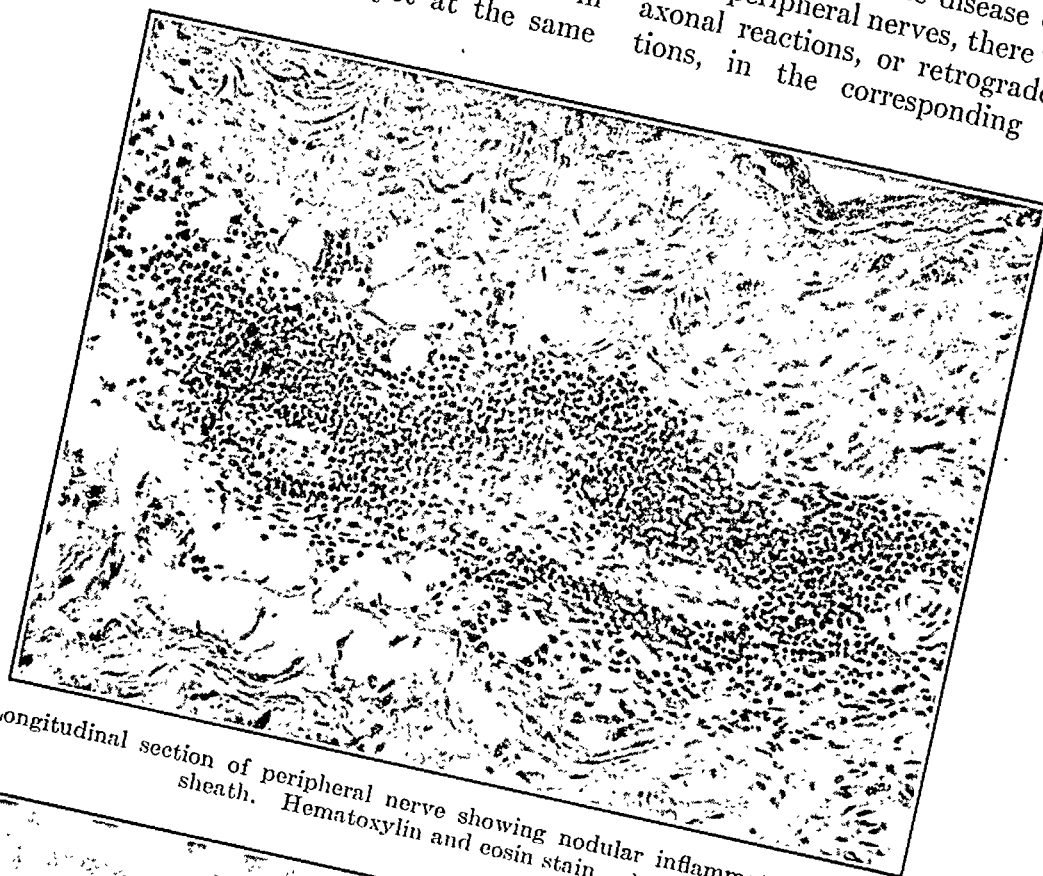


Fig. 3.—Longitudinal section of peripheral nerve showing nodular inflammatory reaction in nerve sheath. Hematoxylin and eosin stain.  $\times 100$ .

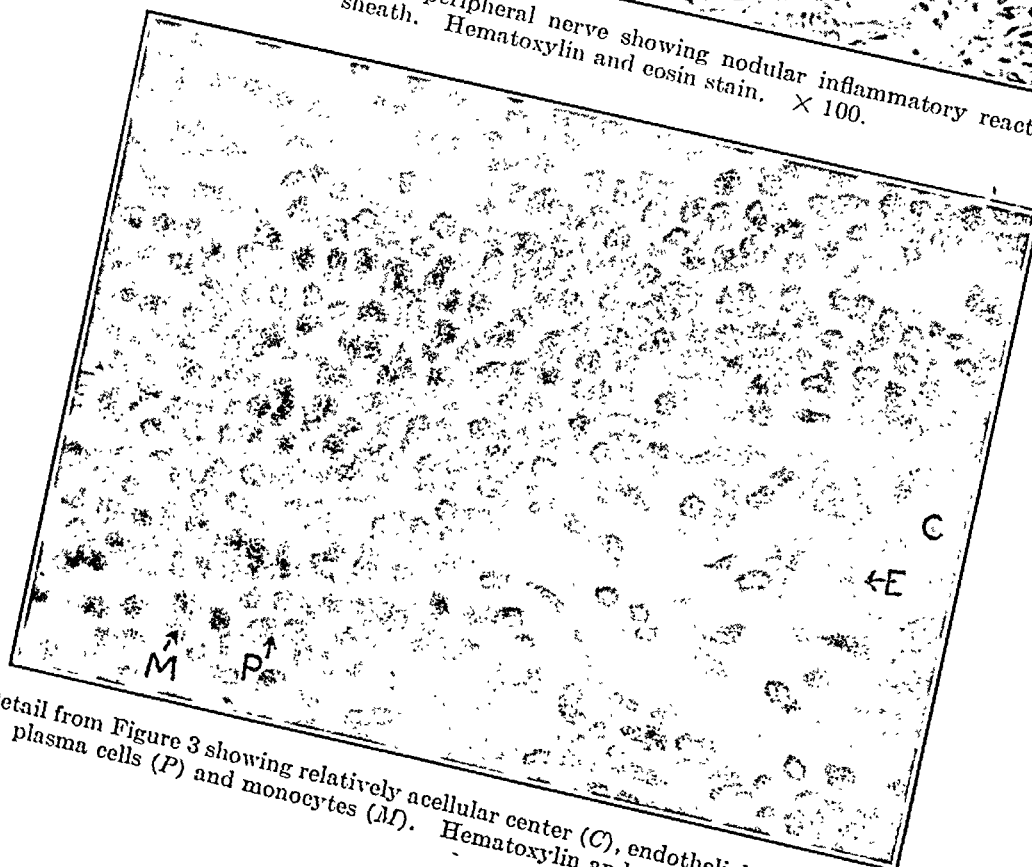


Fig. 4.—Detail from Figure 3 showing relatively acellular center (C), endothelial cells (E), lymphocytes, plasma cells (P) and monocytes (M). Hematoxylin and eosin stain.  $\times 400$ .

bodies. Those of the anterior horn cells have already been mentioned but there were in addition somewhat similar alterations in several of the small number of posterior root ganglia we have examined. These posterior root ganglion cells showed

swelling, central chromatolysis, neuronophagia, increased capsule cells and, in at least 1 case (an 8 year old boy), marked increase in melanotic pigment. Identical changes are recorded by Penny<sup>11</sup> in his histologic study of 6 cases in 1913. Also,

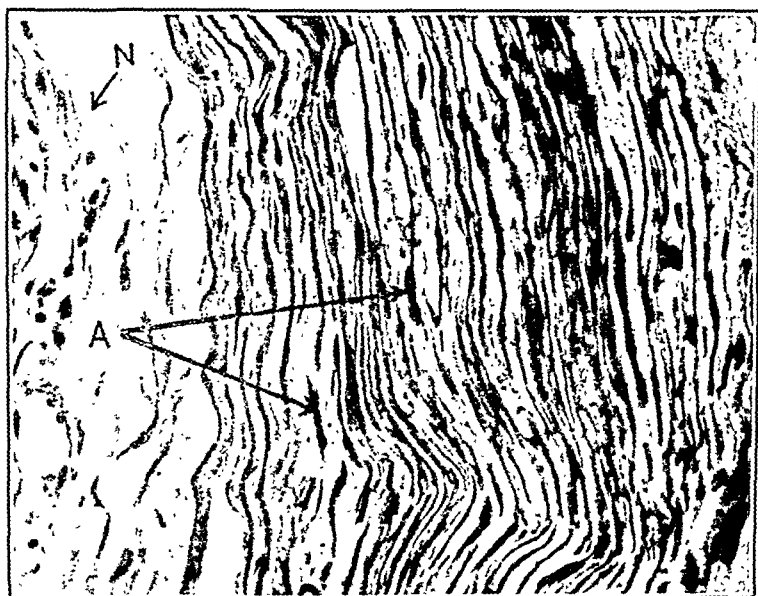


FIG. 5.—Swelling and thickening of axons (A) in close proximity to perineural nodule, edge of which is visible (N). Bodian stain.  $\times 300$ .



FIG. 6. Swollen argentophilic fragments of axon (A). Peripheral nerve. Bodian stain.  $\times 300$ .

as might be expected, alterations were sometimes found in anterior and posterior roots as a possible cause of, or consequent to the degeneration in the corresponding cell bodies. Previous studies have included these findings.<sup>13,39,45,55,57</sup> In a few instances ganglia of the sympathetic chain were examined, but the excessive

pigmentation and interstitial infiltration occasionally seen may have been due solely to age, according to the standards of Kuntz.<sup>35</sup>

As already reported by others,<sup>7,8,14,20,43,52,53</sup> alterations were also found in skeletal muscles. These consisted in collections of lymphocytes, plasma cells and, in the



FIG. 7.—Swelling of the myelin sheath with myelin figure formation. Peripheral nerve. Weil stain.  $\times 300$ .

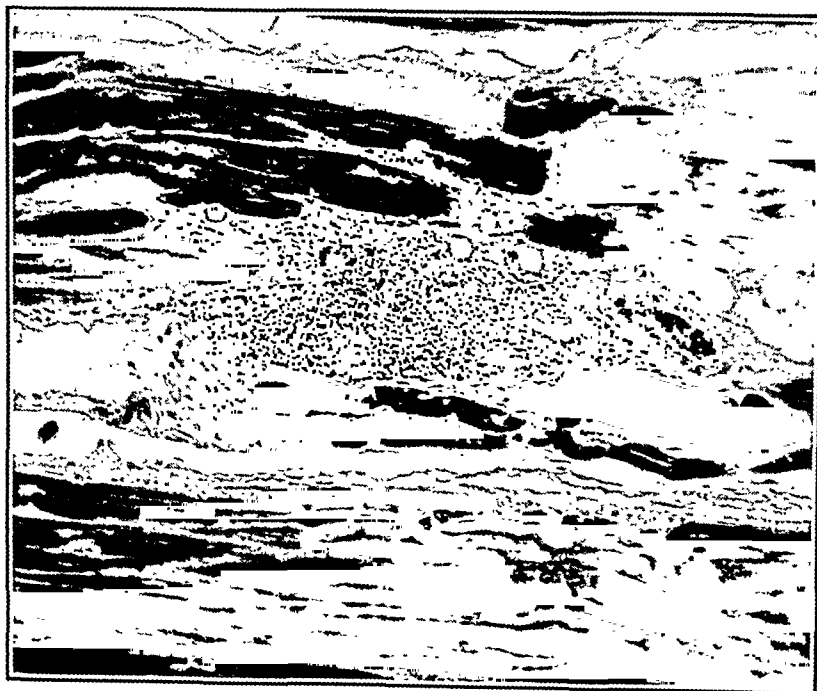


FIG. 8.—Muscle from right calf showing paravascular inflammatory nodule, which consists chiefly of lymphocytes and plasma cells. Eosin-methylene blue stain.  $\times 100$ .

larger foci, occasional epithelioid cells. Such lesions were in the perimysium or endomysium and occurred in 8 out of 14 cases. The lesions varied from definite nodular forms (Fig. 8) to smaller collections of lymphocytes and plasma cells often seen in relation to a blood-vessel. In addition to the inflammatory reaction in the interstitial tissue of the muscle, the muscle fibers themselves were frequently degenerated. This degeneration was characterized by thinning of the muscle fibers, sometimes to such a degree that the sarcolemmal nuclei from opposite sides were touching one another; increase in sarcolemmal nuclei; at times the formation of dense cords of pyknotic nuclei clustered in the midst of a pale, shrunken muscle fiber; loss of cross-striations and increase in connective tissue.

While the inflammatory lesions of the peripheral nerves and muscles suggested specificity, closely corresponding lesions were found in muscle and a nerve in a case of dermatomyositis, in muscle in 1 case of disseminated lupus erythematosus and in a nerve in another, and in muscle from a case of scleroderma. Two patients with rheumatic heart disease, and without evidence of arthritis at autopsy, showed inflammatory changes in peripheral nerves. Since other investigators have reported inflammatory lesions similar to those of rheumatoid arthritis in the muscles in dermatomyositis,<sup>4</sup> scleroderma,<sup>4</sup> rheumatic fever,<sup>7</sup> disseminated lupus erythematosus<sup>43</sup> and anterior poliomyelitis,<sup>12</sup> the existence of characteristic, diagnostic, histologic changes in the neuromuscular system in rheumatoid arthritis remains to be demonstrated.

The results of our histologic studies of the nervous system and muscles in rheumatoid arthritis, combined with those reported in the literature, furnish, however, further evidence of the systemic nature of the disease. Direct involvement of the neuromuscular system by the disease process seems highly likely in the case of peripheral nerves and muscles and possibly accounts for the unexpected

degree of degeneration present in the anterior horn cells. In addition, a reasonable basis is now at hand to explain either wholly or in part the motor and sensory neurologic manifestations of rheumatoid arthritis, as well as the spontaneous skeletal muscle activity demonstrated by electromyographic tracings. Material for histologic examination is available from only 2 patients in whom such muscular activity was demonstrated. Both showed at autopsy, performed  $3\frac{1}{2}$  years and 1 year after the electromyographic studies respectively, inflammatory lesions of a muscle and of a peripheral nerve.

**Discussion.** The general agreement that the muscles of normal individuals in a relaxed state show no evidence of electrical activity<sup>1,28,33</sup> is confirmed by our findings in normal controls. In patients with rheumatoid arthritis, the muscles related to the involved joints may be in an inconstant state of tension. From the nerve-blocking experiments, it is probable that this tension is not produced within the muscle fibers or at the neuromuscular junction but by motor impulses from above the point of block. An additional observation is that there is often only a single motor unit at work in a given area. We have thus far no means of knowing whether or not this tension arises reflexly in response to stimulation of the articular sensory nerve endings. The activity was only rarely associated with conscious discomfort on the part of the patient, and could not be produced by causing pain in the involved joint by squeezing or moving it. Of course the extreme form of this tension, the palpable muscle spasm "guarding" a painful joint has always been assumed to arise reflexly, chiefly because it disappears when the pain is relieved and because of its similarity to muscle spasm arising from disorders of thoracic or abdominal viscera.

The explanation of muscular atrophy in arthritis is not yet at hand, although the theory suggested by Sir James Paget<sup>49</sup> in 1873 that it arises reflexly from painful

stimuli has received the greatest support in several comprehensive reviews of the subject.<sup>2,23,36</sup> Furthermore, it has been shown by animal experiments<sup>10,25,32,44</sup> that muscle atrophy can be prevented or diminished by cutting the posterior roots which carry impulses to the cord from joints in which a chemical or infectious arthritis has been set up. The lack of knowledge of the mechanism by which the muscle atrophy takes place in consequence to the stimuli arising in the joints presents the real difficulty in the full acceptance of this theory. Harding<sup>23</sup> has suggested that it is due to muscular overactivity from abnormally excitable spinal centers and has found increased oxygen consumption in the muscles atrophying sequential to the arthritis. The constant purposeless activity called fibrillation has been brought forward as the cause of muscle atrophy following denervation,<sup>56</sup> although this hypothesis also remains unproven. The muscular tension which we have found in our patients must be present many hours out of the 24. It might conceivably be related, though yet unproven and by a mechanism not explained, to the development of muscular atrophy. However, the existence of continued single motor unit discharges would mean that the tension produced is well below the range of fatigue of the units at work. It is therefore doubtful that muscle wasting could be caused by such activity as we have described.

In view of the demonstration of lesions in the neuromuscular system of patients with rheumatoid arthritis, a more plausible explanation of the spontaneous muscular activity may be available. If we accept this explanation, our nerve-blocking experiments would tend to place their origin somewhere in the proximal part of a lower motor neurone rather than in a muscle, neuromuscular junction or the distal portion of a peripheral nerve. Such a concept is borne out by the finding of a closely similar pattern of single motor unit activity in disorders involving chiefly the lower motor neurone, including ante-

rior poliomyelitis, nerve injuries and infectious polyneuritis.

One objection to this concept lies in the fact that we have recorded single motor unit activity from the muscles of patients with specific infectious arthritis and joint disability due to fixation, where there is no reason to believe that pathologic changes take place in the nerves or muscles similar to those in rheumatoid arthritis.<sup>14</sup> Such patients also demonstrate a rapid onset of muscle weakness and atrophy. Just as the single motor unit muscular activity in lesions of the spinal cord is believed to arise at times reflexly through sensory pathways, it is entirely possible that the activity of like pattern in rheumatoid arthritis may also result from sensory impulses set up in the inflamed joints. This second explanation would also fit in with the results of our nerve-blocking experiments.

It would be premature at this time to attempt to draw any final conclusions as to the relationship between muscle activity, weakness or atrophy and the histologic changes found in the nerves and muscles in rheumatoid arthritis. We shall be satisfied if this presentation and discussion of our findings will encourage the increasing interest in the importance of the neuromuscular system in the total clinical picture in rheumatoid arthritis.

**Summary.** 1. In an attempt to elucidate the mechanism of muscle weakness and atrophy in rheumatoid arthritis, electromyographic studies were performed on patients with rheumatoid and other forms of arthritis. In addition, postmortem histologic observations were made of the central and peripheral nervous system and of the muscles in rheumatoid arthritis.

2. Tracings of voluntary muscle contractions showed no constant deviation from those of normal controls.

3. Synchronization of motor unit leads and spread of tendon reflexes, important electromyographic characteristics of upper motor neurone lesions, could not be demonstrated in patients with rheumatoid arthritis.

4. Involuntary skeletal muscle activity was inconstantly present in 50% of 34 patients with rheumatoid arthritis, consisting usually in a series of regularly recurring diphasic spikes, believed to represent contractions of a single motor unit. A closely similar pattern has been observed in anterior poliomyelitis, peripheral nerve injuries, infectious polyneuritis and spinal cord lesions (tumors and ruptured intervertebral disks).

5. In 8 patients, regularly recurring spikes were not recorded after procaine block of the motor nerve supply to the muscle examined. This finding places their origin above the point of block.

6. In 44 patients with rheumatoid arthritis, the central nervous system showed no specific lesions at postmortem. Alterations usually attributed to aging were more pronounced, however, in the arthritics than in a control group of similar age

distribution. These changes were found especially in the lateral projections of the anterior horns.

7. Lesions were found in the peripheral nerves (in 26 out of 31 cases) and in the muscles (in 8 out of 14 cases) similar to those reported by other observers.

8. Direct involvement of the neuromuscular system by the disease process seems highly likely in rheumatoid arthritis and may explain the neurologic signs and symptoms so prominent in this disease, including muscle weakness and atrophy.

9. The spontaneous skeletal muscle activity in rheumatoid arthritis may also be explained on the basis of pathologic lesions of the lower motor neurones, with corroborative evidence furnished by the closely similar electromyographic pattern found in known disorders of this portion of the nervous system.

The authors are indebted to Miss Margaret Carroll and Mrs. Elizabeth Beresford for technical assistance.

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# PERSISTENCE OF PENICILLIN IN THE CEREBROSPINAL FLUID AFTER MASSIVE INTRAVENOUS ADMINISTRATION

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THE fact that penicillin can surmount the hemato-encephalic barrier and appear in significant concentrations\* in the cerebrospinal fluid was recently demonstrated in a previous publication.<sup>3</sup> It was found that patients receiving 10 million units of penicillin, intravenously, over a 24 hour period, exhibited penicillin in the cerebrospinal fluid in 71.5% of the series, whereas patients receiving 25 million units, intravenously, revealed significant amounts of the drug in 100% of the cases. It was also found that as the dose of the drug was increased, the penicillin level in the cerebrospinal fluid was likewise increased.

In the above study, however, all determinations of spinal fluid concentration of penicillin were made on fluids which had been drawn within  $\frac{1}{2}$  hour after completion of intravenous therapy.

The question, "How long does the penicillin remain in the cerebrospinal fluid?" immediately came to mind. The following study was done to ascertain the duration of time over which penicillin could be detected in cerebrospinal fluid following the intravenous administration of 25 million units of penicillin over a 24 hour period.

A group of 83 patients exhibiting dark-field positive lesions of primary or secondary syphilis was included in this study. Twenty-five million units of penicillin,

contained in 1000 cc. of physiologic saline solution, were administered to each patient by the intravenous route, using drip technique. The pinch clamp was adjusted so that delivery of the 1000 cc. of solution containing the penicillin was distributed equitably over the 24 hour period. A subcutaneous injection of 300 mg. heparin, contained in the "Pitkin menstruum,"<sup>1</sup> was given immediately prior to the initiation of penicillin therapy to circumvent the thrombophlebitis so frequently associated with intravenous administration of penicillin.

A lumbar puncture was performed on each patient only once after the conclusion of therapy. One group of 3 patients was subjected to lumbar puncture 18 hours after the conclusion of penicillin therapy. Another group of 14 patients was studied 12 hours after therapy. Thereafter, additional groups of 14 patients each were examined at 9, 8, 7 and 6 hours after the discontinuation of therapy. A smaller group of 10 patients was examined 5 hours after the completion of therapy, inasmuch as our supply of penicillin was exhausted at this point.

The results of this study are set forth in Table 1. No penicillin could be recovered from patients either at 18 or at 12 hours after completion of treatment.

At 9 hours, however, 1 of the 14 patients

\* Significant levels for the purposes of this paper are 0.01 to 0.075 unit per cc. as reported by McDermott, Benoit and DuBois<sup>2</sup> to be the "effective level" for *Treponema pallidum*.

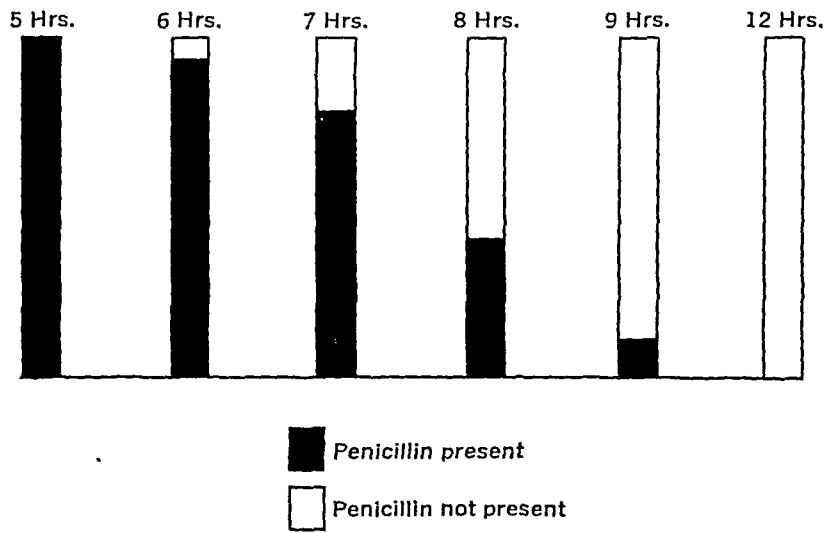
studied revealed a significant level. Thereafter, as the interval between the time of completion of treatment and the time of lumbar puncture was shortened, the frequency of appearance of appreciable penicillin levels varied inversely. Thus, at 5 hours, 100% of the patients studied demonstrated significant cerebrospinal levels of penicillin.

tions of the nervous system is generally recognized. A safe, effective mode of directing the drug to the site of the pathologic process, therefore, assumes great importance, and it follows that the length of time over which the drug will remain at the site desired is of great moment. No relationship could be established between age, weight, or sex in either the

TABLE 1.—PENICILLIN LEVELS IN CEREBROSPINAL FLUID AFTER TREATMENT  
OXFORD UNITS PER Cc.

5 hrs.	6 hrs.	7 hrs.	8 hrs.	9 hrs.	12 hrs.
0.04	0.02	0.1	0.05	0	0
0.06	0.025	0	0	0	0
0.025	0.06	0.03	0	0	0
0.05	0.06	0	0	0	0
0.06	0.03	0.03	0	0	0
0.1	0.06	0.02	0.025	0	0
0.05	0.1	0.025	0.05	0	0
0.05	0.1	0.1	0.025	0	0
0.3	0	0.05	0	0	0
0.03	0.04	0.05	0	0	0
	0.025	0.025	0.025	0	0
	0.02	0.025	0	0	0
	0.05	0	0.025	0	0
	0.04	0.03	0	0.02	0
Percentage of Fluids Showing Penicillin					
100%	93%	78%	43%	7%	

TABLE 2.—RELATIONSHIP BETWEEN TIME FOLLOWING COMPLETION OF TREATMENT AND FREQUENCY OF DETECTION OF PENICILLIN IN CEREBROSPINAL FLUID



Each group comprises 14 patients with the exception of the "5 Hrs." group in which there were 10 patients.

Table 2 graphically illustrates the relationship between the length of time elapsing following the completion of therapy and the frequency of detection of penicillin in the cerebrospinal fluid.

**Comment.** That penicillin is a most effective agent in the treatment of infec-

concentration or the frequency of appearance of penicillin in the cerebrospinal fluid after given periods of time, following completion of therapy.

**Summary.** 1. A group of 83 patients with dark-field positive syphilis were given

25 million units of penicillin by continuous intravenous drip over a 24 hour period.

2. Penicillin activity in the cerebrospinal fluid of these patients was determined at 18, 12, 9, 8, 7, 6 and 5 hours after completion of treatment.

3. Penicillin could be detected in the cerebrospinal fluid of all patients whose lumbar puncture was performed 5 hours after completion of treatment; the highest

levels being 0.3 Oxford units per cc., and the lowest being 0.04 Oxford units per cc.

4. Inverse proportion was observed between time elapsed after completion of treatment and percentage of patients presenting penicillin in the cerebrospinal fluid.

5. No penicillin was detectable in the cerebrospinal fluid of patients 12 hours after the completion of treatment.

We are indebted to Mr. John L. Smith of Charles Pfizer & Co., for his keen interest, valuable suggestions and constant coöperation. We were able, through him, to obtain the generous supply of penicillin utilized in these experimental studies. We wish to express our appreciation to Miss Helen Zaborowski for technical assistance.

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## TWO COEXISTENT STRAINS OF VIRIDANS STREPTOCOCCUS ISOLATED FROM BLOOD CULTURES BY PENICILLIN SENSITIVITY TESTS\*

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THE advent of penicillin therapy in the treatment of subacute bacterial endocarditis should have a salutary effect in stimulating more careful bacteriologic studies of the organism. With increased experience in the effective use of penicillin to achieve clinical cures in these cases, it now seems of paramount importance to investigate more critically the possible reasons for the reappearance of bacteria during, or shortly after completion of, treatment presumed to be adequate. Most of the larger series of cases have included a small percentage falling into this group, which have frequently yielded to increased therapy. Two possible reasons have been considered from time to time in the literature: (1) the development of an acquired resistance to penicillin by the particular strain involved; (2) the possible presence of more than 1 strain at the time of treatment. The first has received wide, and on the whole uncritical, acceptance; the second has only occasionally been suggested, most recently by MacNeal and Blevins.<sup>4</sup> Believing that the latter possibility has not received the careful consideration it warrants, we submit the following report of 2 coëxistent strains of streptococci with widely divergent sensitivities to penicillin, found in each of 2 successive blood cultures drawn from a recent patient with subacute bacterial endocarditis.

The first evidence of 2 strains was observed in the course of a rapid estimate of sensitivity to penicillin routinely done in this laboratory by placing filter paper disks impregnated with known dilutions of a penicillin standard on blood agar

plates thinly streaked with the first identifiable growth obtained. Since the original culture had taken 72 hours to develop in broth flasks, and subculture growth on blood agar plates was scanty, duplicate test plates were made; 1 for routine aërobic culture at 37° C., 1 for 10% CO<sub>2</sub>. In 24 hours the culture under reduced oxygen tension had grown well, outside of a sharply defined clear zone surrounding the filter paper disk, which indicated a sensitivity of 0.03 Oxford units. Normal aërobic incubation had only produced a scanty, irregular growth in the outer areas of the second test plate at this time. Both plates were returned for further incubation under normal oxygen tension. Careful examination after 48 hours revealed similar, well-defined zones of inhibition now clearly apparent on both plates, and in addition 2 and 3 single colonies, respectively, growing at various points well within the clear zones.

Subcultures from these isolated colonies grew luxuriantly in 24 hours under normal atmospheric conditions. The simultaneous subcultures made from the first growth observed, selected just beyond the edge of the clear zone to minimize any differences due to unequal exposure to penicillin, again required 10% CO<sub>2</sub> for optimal growth in 24 hours. Blood agar plate sensitivities to penicillin were repeated for each of the 2 strains thus isolated. The colonies subcultured from outside the zone of inhibition again had a sensitivity of 0.03 Oxford units, and will hereafter be referred to as the C-PS strain. In marked contrast, the paper disk method indicated a probable sensitivity of 5 Ox-

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ford units for the second strain, subcultured from the scattered colonies within the original clear zone. The latter will be referred to as the C-PO strain. Both sensitivities were subsequently confirmed by a turbidity method. Blood agar plate sensitivities, repeated with each strain on several occasions, failed to produce any variation in the growth characteristics or sensitivity of either one, or any other colonies within the clear zone of the C-PS strain which might suggest the development of a penicillin resistant variant of the original strain. The 2 strains were similarly isolated from a second culture, taken 24 hours later.

Cultural and biochemical evidence further confirmed our impression of the presence of 2 distinct strains, and the differential characteristics remained unchanged over a period of 3 months, except for relatively greater ease in growing the C-PS strain due to prolonged subculture on artificial media. Both strains produced alpha hemolysis on (human) blood agar plates, and could be roughly classified as belonging to the viridans group of streptococci, although each had a distinctively different appearance. The C-PS strain consistently produced a flat, dark forest-green growth. Under the colony scope this resolved itself into very small, discrete, smooth, moist, pyramidal colonies, dark in color, and surrounded by a fairly extensive area of deep green discoloration with partial destruction of the erythrocytes. The C-PO strain was equally consistent. Larger colonies, smoothly rounded, glistening, paler yellow-green tending toward confluence, and a moderate area of discoloration without visible destruction of the erythrocytes were formed, which browned somewhat with age. Further pertinent data can be summarized as follows: dextrose, lactose, maltose, mannite, salicin, sucrose were fermented in 24 hours by the C-PO strain. The C-PS strain fermented none in a week, although good growth was supported by the medium. Neither attacked inulin in 1 week. Medium for optimum growth of

the C-PO strain was ascites-dextrose-veal broth, although a simple veal broth supported it adequately. The C-PS strain continued to require Brewer's medium for optimum growth.

Lancefield typing sera were not available to us at the time of this study, and the C-PS strain spontaneously failed to survive routine subculture after 3 months. However, the diversity of the action on blood agar, sensitivity to penicillin, and sugar fermentation reactions appear to be sufficient to fulfill Sherman's criterion that "a difference in 5 characters is ample to tell us that 2 bacteria are not the same."<sup>5</sup> No further positive blood cultures were obtained, as high dosage penicillin therapy, based on the indicated sensitivities, was immediately instituted, the patient became bacteria-free, and has remained so to date (11 months). Because of the preponderantly heavy growth of the C-PS strain, we were not successful in isolating the individual strains by any other means than the difference in sensitivity to penicillin.

Since the early work of one of us<sup>3</sup> in isolating 2 coexistent strains of viridans streptococcus from the same heart valve lesions, we have been interested in the incidence of mixed infections in septicemia and bacterial endocarditis. We feel that the simultaneous presence of more than 1 strain of streptococcus is quite possible, and a definite factor to be considered in the bacteriologic diagnosis of subacute bacterial endocarditis. Fleming introduced the principle of sensitivity to penicillin as a differential factor in isolating different organisms in 1929, in his work with *H. influenzae*.<sup>2</sup> Within the past few years it has been rather widely developed as a means of securing positive cultures for the diagnosis of pertussis. The use of penicillin directly on the culture plate for this purpose has most recently been discussed by Bradford, Day and Berry<sup>1</sup> but so far as we have been able to determine this is the first application of the principle to the isolation of 2 infectious strains of streptococcus occurring

simultaneously in a case of bacterial endocarditis. Such a condition is particularly important when a heavy or antagonistic growth of a relatively sensitive strain may completely mask the presence of a more resistant strain, unless positive cultures are carefully studied with this in view. Should oversight lead to inadequate penicillin therapy, clinical relapse with re-appearance of the more resistant strain could be expected.

**Summary.** 1. Two coëxistent strains of *Strep. viridans* were isolated from a case

of subacute bacterial endocarditis only because of widely divergent sensitivities to penicillin.

2. The undiscovered presence of more than 1 infective strain of streptococcus can be a factor in causing apparent relapse of patients with subacute bacterial endocarditis, following penicillin therapy.

3. The Oxford cup, or filter paper disk modification, for determining penicillin sensitivity may provide a valuable method for isolating individual strains of organisms from a mixed culture.

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# THE SPONTANEOUS OCCURRENCE OF NEW BACTERIAL INFECTIONS DURING THE COURSE OF TREATMENT WITH STREPTOMYCIN OR PENICILLIN\*†

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THE use of antibiotic agents with highly specific, selective activity has solved many of the difficulties encountered in the treatment of infectious diseases. However, many new problems have been created; some of these arise because the lives of patients are prolonged sufficiently to allow time for the development of complications of the original disease; others are the result of accidents occurring during the administration of these drugs, such as the introduction of new bacteria; some arise as the result of the use of a drug with no action against the infecting organism. It is with one of these problems, the appearance of new infections during the course of treatment with such agents as penicillin and streptomycin, that this paper concerns itself.

Although both penicillin and streptomycin are highly antibacterial, this activity is more or less specific; thus, penicillin is active mainly against gram-positive bacteria, whereas streptomycin exerts its greatest effects against members of the gram-negative group. Although organisms susceptible to each of these agents show varying degrees of resistance, on the whole most of the susceptible bacteria can be eliminated if an adequate dose of either of the antibiotic agents is given. During the course of therapy with streptomycin or penicillin, in addition to an effect on the specific organism responsible for an infection, alterations in the bacterial flora in various parts of the body may occur; thus gram-positive bacteria may be eliminated from the nasopharyngeal flora when penicillin is administered and gram-nega-

tive ones when streptomycin is given. Lipman, Coss and Boots,<sup>1</sup> in a study of the throat and intestinal flora of rheumatoid arthritis cases to whom penicillin was administered daily over a period of months demonstrated a rapid and striking change. The throat cultures of all of the patients revealed a predominance of gram-positive diplococci sensitive to penicillin prior to antibiotic therapy. During the course of treatment, gram-negative organisms, mainly *E. coli*, were found to be predominant. Less striking though definite changes in the intestinal flora also took place.

It is possible that such alterations in the distribution of organisms in sites of the body where a mixed flora is usually present may occur in many patients who receive therapy with one of the specific antibiotic agents. In most cases, such changes in the bacterial population with suppression of certain groups of bacteria and increase in the number of others probably leads to no untoward result, and the patient's recovery is not affected. In other cases, however, such alterations in the flora result in the rapid growth of virulent bacteria, which may have been present originally only in very small numbers, and which were not susceptible to the antibiotic agent administered. If the general resistance to infection be depressed, new infections may occur following such a change. In the cases described below, the use of either streptomycin or penicillin resulted in the elimination of one group of bacteria and allowed another which was probably present in small numbers in certain sites to become numeri-

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cally predominant and to invade the tissues and produce new disease.

New infections arising during the course of antibiotic treatment may have a different pathogenesis than the one just described. Organisms that are not susceptible to the specific agent being used may be introduced accidentally (from the skin or from contaminated apparatus) during the administration of the antibiotic substance into the pleural, peritoneal, synovial, or lumbar spaces or into the muscles or blood stream in the course of venipuncture and intramuscular injections, and may produce new infections at a time when the original disease is responding well to therapy. Infection with gram-negative bacteria during the course of penicillin treatment, such as gluteal abscess due to *E. coli* and infections of pleural fluids with *Ps. æruginosa* or with *P. vulgaris*, have been seen in this hospital. This type of new infection is not the result of a change in the normal bacterial flora of tissues, however, but results from the introduction of new organisms accidentally during the manipulations incident to the proper administration of the antibiotic agents. This type of new infection is not described in this paper. Only those cases in which alterations in the normally occurring bacterial flora led to the establishment of new infections are discussed.

In our study of the treatment of scarlet fever with penicillin, Type B and untypable strains of *H. influenzae* that could not be detected on the original nasal and pharyngeal cultures became the predominant organism in the nasopharynx of a large number of patients after *Strep. pyogenes* had been eradicated. This was probably due to the fact that there was an increase in the carrier rate of *H. influenzae* in this part of the country during the past winter as evidenced by detection of a larger number of individuals harboring this bacterium and by an increase in the incidence of *H. influenzae* meningitis. The failure to isolate this organism from the throat cultures before penicillin was administered was probably

due to the fact that they were present only in very small numbers. With reduction in the gram-positive organisms as the result of treatment, the gram-negative ones increased in numbers, and *H. influenzae*, *E. coli* and members of the Neisseria group became predominant. In practically all the patients who showed this type of change in the nasopharyngeal flora, no complicating infections were seen. However, in 1 case, this type of change in bacterial flora resulted in pneumonia and bacteremia due to *H. influenzae* and, in another, led to severe bronchitis and pneumonia due to *K. pneumoniae*. These cases are described below.

**Case Reports.** CASE 1. A 4 year old white boy was admitted to the hospital because of pneumonia following measles. Six days previously, he had had a temperature of 104° F. and Koplik's spots. The next day, a typical morbilliform rash was present over the entire body. While the eruption was fading and the patient was apparently getting better, there was a sudden rise in temperature. A diagnosis of pneumonia was made and the child was sent to the hospital.

Physical examination on admission revealed an acutely ill boy who was breathing rapidly, with flaring of the alæ nasi, and had a non-productive cough. The temperature was 105.8° F., the pulse 160, the respirations 42, and the blood pressure 110/64. The skin showed a diffuse fading measles rash. The pharynx was slightly reddened but showed no other abnormalities. Examination of the lungs revealed widespread fine, crackling moist râles. The remainder of the physical examination was within normal limits.

The urine on admission was clear except for 1+ albumin. The hemoglobin was 10.6 gm. per 100 cc., and the white cell count 8300, with 62% neutrophils, 34% lymphocytes, 3% monocytes and 1% eosinophils. A blood culture was sterile. The nose and throat revealed a preponderance of non-hemolytic *Staph. aureus*, but alpha streptococci, diphtheroids, and *N. catarrhalis* were also present.

Penicillin in a dosage of 15,000 units every 3 hours was administered immediately after admission, and continued for



18 days. The temperature remained elevated to high levels during the first 2 days and there appeared to be some spread of the pneumonic process. The quantity of penicillin was increased, therefore, to 25,000 units every 3 hours. Following this, there seemed to be some improvement and the temperature fell to 101° F., but on the 5th hospital day suddenly rose to 104° F. The patient appeared considerably more ill, and the pneumonia seemed to have spread further. Although nose and throat cultures were made daily, *H. influenza*, Type B, was isolated in almost pure culture from these sources for the first time on the 4th day. It had not been detectable in the cultures made before this time. A blood culture taken on the 5th day revealed the influenza bacillus. The white cell count rose to 16,500, with 84% polymorphonuclear leukocytes, most of which were young forms. On the 5th day, the cold agglutinin titer of the blood was 1:64.

Because of the failure to respond to penicillin and the recovery of *H. influenza* from the throat and blood late in the course of the disease, it was thought that the patient had had an atypical viral bronchopneumonia which had become complicated by secondary infection with *H. influenza*. Therefore, 1 gm. of streptomycin per day was administered in divided doses every 3 hours intramuscularly, and penicillin was stopped. The temperature fell promptly to normal levels for 1 day and then rose again to 105° F., with an increase in the white blood cell count to 29,450. At this time, marked redness, swelling, heat and tenderness were noted in the lateral aspect of the right thigh at the site of a needle puncture for hypodermoclysis. Because of the presence of this subcutaneous infection, penicillin treatment was resumed. The 2 antibiotic agents were administered together and the temperature promptly returned to normal, where it remained for the remainder of the hospital stay. The area of inflammatory reaction in the leg gradually subsided, the changes in the lungs cleared, and the respiratory rate fell to normal. The patient was completely well when discharged from the hospital 27 days after admission.

CASE 2. A 53 year old white man was admitted to the hospital with a diagnosis of faucial diphtheria. His illness had begun

1 week previously with a sore throat; this became rapidly and progressively worse until he was extremely weak, unable to swallow and had moderate dyspnea. No treatment was given except for 50,000 units of penicillin every 4 hours for 3 days prior to admission.

Physical examination revealed a well-developed, moderately obese man who appeared acutely ill and was breathing with some difficulty. The temperature was 102°, pulse 108, respirations 30, and blood pressure 110/80. The pharyngeal mucosa was covered by a thick grayish white exudate which extended onto the soft palate and over both tonsillar fossæ, and covered the entire uvula. The breath had a pungent, fetid odor. There was limitation of motion of the left side of the chest and dullness to percussion over the entire left lung anteriorly and posteriorly; the breath sounds were markedly diminished just below the scapula and were barely audible over the left base. No bronchial breathing was heard and only occasional coarse râles were audible. The lung findings were interpreted as due to extension of diphtheritic membrane down the trachea and into the left lung, since the patient was very hoarse. The trachea was in the midline. The heart was within normal limits except for a rate of 102. The remainder of the physical examination was not remarkable except for moderate cyanosis of the nail beds and lips.

The urine had a specific gravity of 1.022, and contained 80 to 100 white blood cells per high power field on admission but was within normal limits thereafter. The white blood cell count was 29,700, with 79% neutrophils, 18% lymphocytes, 2% monocytes and 1% basophils. A blood culture was negative. Culture of the nose and throat revealed large numbers of hemolytic *Staph. aureus*, *C. diphtheriæ* and Type 14 pneumococcus. *K. pneumonia* was not found in the nose or throat on admission.

The patient was given 100,000 units of diphtheria antitoxin immediately after admission, and started on a regimen of 30,000 units of penicillin every 3 hours intramuscularly. In the next few days, the temperature gradually returned to normal and improvement in the clinical status took place; during this time several pieces of tough diphtheritic membrane were coughed

up. On the 2nd hospital day, following a violent coughing spell, the patient developed interstitial emphysema, the air being present subcutaneously over the upper part of the chest, neck and face; this disappeared within 24 hours. On the 5th day, dyspnea became more marked and there were signs of fluid in the left chest. Thoracentesis yielded 600 cc. of sterile serosanguineous fluid which contained 15,000 erythrocytes and 750 leukocytes, 42% of which were neutrophils, 39% lymphocytes and 19% epithelial cells. The total protein was 3.62 gm. per 100 cc. and the fluid clotted on standing. One day prior to chest tap (4th day), the patient began to cough up thick, purulent, blood-streaked sputum which contained large numbers of *K. pneumoniae* and *E. coli*. None of the throat cultures which had been done previously (daily) had ever revealed any gram-negative organisms. Bacteriologic examinations of the throat and sputum subsequent to the 4th day showed only *E. coli* and the Friedländer's bacillus. Many fine and coarse moist râles were present in both lungs continually from the 4th day, and cough and expectoration of bloody, purulent sputum increased. On the 6th day, the patient began to have more difficulty in breathing, gradually went into peripheral vascular collapse, and in spite of intensive therapy, including 0.5 gm. of streptomycin given intramuscularly every 3 hours, expired early on the 7th hospital day.

Electrocardiograms taken revealed no abnormalities on the day of admission, auricular premature systoles in all leads on the 4th day, and right bundle branch as well as complete heart block on the day preceding death.

*Postmortem examination* showed a diffuse myocarditis which grossly resembled that of diphtheria. The mucosa of the entire tracheobronchial tree was markedly reddened and there was a small amount of purulent exudate in the bronchi. The lungs were the seat of an early bronchopneumonia. Culture of numerous areas in the pulmonary tissues revealed only *K. pneumoniae*. Two blood cultures taken on the day of death were sterile.

CASE 3. A 3 year old girl was admitted to the hospital because of fever and abdominal pain. Two and a half years prior to admission she had had a "kidney infec-

tion," from which she recovered in 23 days. Seven weeks before coming to the hospital she had uncomplicated pertussis. Six hours before admission, there was a sudden onset of abdominal pain and vomiting. The temperature was elevated to 101.2° and the patient was brought to the hospital.

On admission the temperature was 99° F., the pulse 160 and the respirations 26. Physical examination was entirely within normal limits except for slight distention of the abdomen and generalized abdominal tenderness, somewhat more marked on the right. Peristaltic sounds were diminished. No tenderness could be detected in the costovertebral angles. The white cell count was 24,100, with 84% neutrophils and 16% lymphocytes. Examination of the urine revealed a specific gravity of 1.020, 2+ albumin, and 50 to 60 white cells per high power field, in a catheterized specimen. The hemoglobin was 11 gm. per 100 cc. Culture of the urine revealed *H. influenzae*, which was neither Type A or B.

Streptomycin, 125 mg. every 3 hours, was administered intramuscularly for 5 days. The temperature remained normal during the entire course of treatment, and the urine was sterile 24 hours after beginning therapy with the antibiotic agent. The leukocytes in the urine decreased rapidly until, on the 5th day, there were only 1 or 2 per high power field; the albuminuria disappeared. The white cell count fell to 9100 by the end of 10 days. The temperature throughout the hospital stay was normal except for the 6th and 19th days, when it rose to 100.4° and 100.8°, respectively. On the 7th day, the number of white cells in the urine increased to 30 to 40 per high power field. Thereafter, pyuria persisted, with 12 to 20 white cells per high power field in catheterized specimens. Simultaneously with the recurrence of pyuria, non-hemolytic *Staph. aureus* was cultured from the urine; this organism was isolated a number of times during the remainder of the hospital stay.

Because of the recurrent pyelonephritis, the patient was referred to another hospital for complete study of the renal tract.

CASE 4. A 10 month old girl was referred to the hospital because of drowsiness of 2 days duration and vomiting and fever (103° F.) and stiffness of the neck for 24 hours.

The striking findings on physical examination at admission were extreme restlessness, tachypnea, bilateral internal strabismus, stiffness of the neck and back, and positive Kernig's sign. The temperature was 105.6° F., the pulse rate 150 and respiration 44 per minute. The urine was within normal limits. The white cell count was 10,850, with 70% neutrophils, 29% lymphocytes and 1% monocytes. The spinal fluid was under increased pressure and contained 18,250 cells, 80% of which were neutrophils; the protein was 114 mg. per 100 cc., and the sugar 26 mg. *H. influenzae*, Type B, was present in both the spinal fluid and blood. Cultures of the nose and throat revealed diphtheroids, alpha streptococci, and few colonies of *Staph. aureus* and *N. catarrhalis*.

Immediately after admission, treatment with streptomycin, 0.1 gm. every 3 hours intramuscularly, was started and continued for 5½ days. It was then omitted for 2 days following which 1.2 gm. was administered in the next 30 hours. Fifty mg. of the antibiotic agent were instilled into the spinal canal on admission, and 0.025 gm. given every 24 hours thereafter for the next 10 days. The blood and spinal fluid were cleared of *H. influenzae* 24 hours after treatment was started and remained sterile for the rest of the hospital stay.

There was moderate improvement in the clinical condition, and the temperature returned to normal on the 5th day, but coma and twitchings persisted. Bacteriologic examination of the nose and throat revealed that on the 5th day and every day thereafter, a pure culture of hemolytic *Staph. aureus* was present. The temperature rose to 102° F. on the 8th day and remained at high levels for the rest of the course. On the 9th day, moist crackling râles were heard throughout both lung fields, and Roentgen ray examination revealed diffuse bilateral bronchopneumonia. Penicillin, 120,000 units per day, was given intramuscularly for 3½ days but the coma persisted, convulsions became more frequent and severe, and death occurred on the 12th hospital day. Cultures of the blood during the last 2 days of life revealed hemolytic *Staph. aureus*.

At autopsy the brain was essentially normal except for 2 small plaques of fibrin, 1 on each of the cerebral hemispheres, from

which no bacteria were recovered. The lungs were the seat of a very diffuse, confluent bronchopneumonia from which coagulase-positive, hemolytic *Staph. aureus* was isolated.

CASE 5. A 4 month old boy was sent to the hospital because of convulsions of 24 hours duration. The illness began about 10 days prior to admission, when after a mild upper respiratory infection, he suddenly developed a temperature of 103° F. Treatment with one of the sulfonamides produced a moderate degree of improvement, but on the day before entry the patient began to have frequent episodes of generalized convulsions. He was admitted to another hospital where lumbar puncture revealed a cloudy spinal fluid containing gram-negative pleomorphic bacteria and was therefore referred to the Haynes Memorial Hospital.

On admission to this hospital, the temperature was 102.2° F. and the respirations 32. The positive physical findings were marked generalized rigidity, bulging of the anterior fontanelle, slight reddening of the tympanic membrane on the right, a small amount of purulent exudate and reddening of the mucous membrane of the nose, marked stiffness of the neck and back, and positive Kernig's sign.

The urine was essentially normal. The white blood count was 8520, with 46% neutrophils, 49% lymphocytes, 3% monocytes and 2% basophils. The hemoglobin was 11 gm. per 100 cc. Lumbar puncture revealed an initial pressure of 280 and the spinal fluid contained 36,400 cells, 91% of which were polymorphonuclear leukocytes; the sugar was 30 mg. per 100 cc., and the protein 50 mg. Direct examination and culture of the spinal fluid revealed *H. influenzae*, Type B. Bacteriologic examination of the blood and nose yielded the same organism. Throat culture revealed *N. catarrhalis*, diphtheroids, alpha streptococcus and a few colonies of *Staph. aureus*.

The patient was given 0.05 gm. of streptomycin every 3 hours intramuscularly, and 0.02 gm. of the drug was administered intrathecally every 24 hours except for the 2nd, 3rd and 4th days, when it was given every 12 hours. Intramuscular therapy was continued for 8 days and intrathecal treatment for 13 days. The causative organisms disappeared from the spinal

fluid and blood within 24 hours after streptomycin was exhibited, and the patient appeared to be making a rapid recovery. On the 7th day, there was a sudden elevation of temperature to 104.6° F., and the blood and spinal fluid were found to contain coagulase-positive hemolytic *Staph. aureus* every day from the 7th to the 14th day. *Staph. aureus* was present in pure culture in the nose and pharynx for the first time on the 5th day and daily thereafter until intensive penicillin therapy was administered. On the 10th day, a punctate erythematous rash resembling scarlet fever made its appearance; this increased in intensity for 48 hours and then began to fade, disappearing completely after 6 days. Because of the persistence of *Staph. aureus* in the spinal fluid and blood, penicillin was given in doses of 25,000 units every 24 hours intrathecally and 15,000 units every 3 hours intramuscularly. Because this treatment did not produce clearing of the blood stream in 6 days, the amount of antibiotic agent given by both routes was doubled. Thereafter, the organisms decreased markedly in numbers in the throat and disappeared rapidly from the spinal fluid and blood. The patient made an uneventful recovery.

**Discussion.** Five cases have been described in which, during the course of specific antibiotic therapy, there developed new infections due to organisms that were not susceptible to the agent with which the primary disease was treated. In 1 patient who probably had atypical viral pneumonia, the administration of penicillin resulted in an overgrowth of *H. influenzae* in the pharynx, followed by an invasion of the blood and respiratory tract. In another individual, treatment of faucial diphtheria was complicated by the occurrence of pneumonia due to the Friedländer bacillus. The other 3 cases were treated with streptomycin for *H. influenzae* infections, and 1 developed bronchopneumonia with bacteremia, another meningitis with bacteremia, and a third recurrent pyelonephritis, all due to hemolytic *S. aureus*.

The mechanism by which this type of infection occurs is not completely clear.

However, in 4 of the patients there was a remarkable change in the bacterial flora in the nose and throat before new infection developed. Organisms that were apparently present in such small numbers that they were not detected early in the course of the disease increased in number after treatment with penicillin or streptomycin and invaded the tissues. That the new infections were not merely the result of numerical increase of one of the normal inhabitants of the nose and throat is evidenced by the fact that changes in the nasopharyngeal flora following the use of either antibiotic substance were frequently observed without a resultant new infection. It is possible that in some persons, a high degree of bacterial antagonism exists in areas like the nasopharynx and that certain groups of bacteria are kept in check by others. So long as this normal relationship is not disturbed, the numbers and invasive ability of some of the organisms may be kept below a critical level; when, however, some of the bacteria are removed as a result of contact with an antibiotic agent of high specificity, those organisms that are unaffected by the drug increase sharply in number and possibly in virulence. This phenomenon may be entirely due to an increase in numbers of bacteria if the microorganisms are of sufficiently high virulence. These new infections were seen mainly in young children and in 1 middle-aged adult who had had a serious infection and intoxication for 1 week before antibiotic therapy was started. Age, therefore, may be a determinant factor. Other factors that tend to produce lowered resistance, such as chronic debilitating disease, senility, etc., may also be of importance.

The type of organisms normally present in the pharynx is dependent to some degree on the general distribution of various bacteria in the population during certain seasons of the year. This will determine, in part, the organism that produces a new infection during the course of antibiotic therapy; for example, in the summer season the carrier rate for *H. influenzae*

is low and the chance that invasion by this organism will occur as a result of penicillin treatment is less than it is in the winter. *Staph. aureus* is present in the pharynx of most persons at all times, so that the seasonal factor probably plays only a minor rôle in production of disease by this organism in patients who receive streptomycin.

The spontaneous occurrence of new infections due to non-susceptible organisms during the course of penicillin or streptomycin therapy raises the question of the use of either of these drugs in instances where the exact bacteriologic diagnosis is unknown, because patients may be exposed to the added danger of superimposed bacterial disease without any benefit to the primary process. For example, the treatment of virus infections with either streptomycin or penicillin may be dangerous because these drugs have no effect on the primary disease, and may allow organisms that are normally present on various tissues and are not susceptible to their activity to grow profusely and invade. The occurrence of this type of secondary infection is a strong argument for limiting the use of the antibiotic agents to those cases in which bacterial disease is proven by isolation of the causative agent or to those in which the possibility of bacterial infection is very strong.

Although it might appear that the availability of such agents as streptomycin and penicillin has reduced the necessity for careful bacteriologic studies in patients with infectious diseases, the exact opposite is the case. The highly specific antibacterial activity of these drugs necessitates exact identification of the causative agents of the infections for which they are used, and the need for careful bacteriologic study is greater now than it was prior to the advent of the antibiotic substances. This applies not only to the period of the disease before treatment is started but also to the time during which therapy is being given, lest the manifestations of new infections of the type de-

scribed in the cases reported above be misinterpreted as due to failure of the original disease to respond to the drug being used. Frequent bacteriologic examination of the blood and of the nose and throat of patients who are being treated with an antibiotic agent, even though they seem to be progressing well, is to be highly recommended because a marked increase in numbers of an organism in the nasopharynx frequently precedes its invasion of the tissues by at least 24 hours. The discovery of a preponderance of *H. influenzae* or *S. aureus* in the nasopharyngeal flora during the course of penicillin or streptomycin treatment should put the physician on guard for a complicating infection due to either of these organisms, particularly if the patient is a young child.

Since new infections may occur spontaneously during the administration of penicillin or streptomycin, the question may be raised whether or not these 2 agents should be given simultaneously to patients who are particularly susceptible to such an event, namely the very young or very old, or those with chronic debilitating disease. The combined use of the antibiotic drugs in a shotgun fashion with the implication that bacteriologic examination is then not necessary can only be decried. Although each of these agents is, on the whole, non-toxic, certain patients may become sensitized to them to the point where they cannot be used. Treatment with a combination of both drugs with an untoward sensitizing reaction may preclude the use of either agent some time later in the patient's life when his survival may depend on them. To advocate the employment of a combination of penicillin and streptomycin would result in even greater misuse of these drugs than they are at present subjected to, and would only further their use in many diseases in which there is no infectious basis.

**Conclusions.** 1. Five cases of complicating infections occurring during the course of treatment with antibiotic agents,

2 following penicillin therapy and the others following streptomycin treatment, have been described. In all of these the second infection was produced by organisms normally present in the nasopharynx and was not the result of the accidental introduction of bacteria.

2. The development of spontaneously occurring new infections during the course of penicillin or streptomycin therapy is a

constant danger and must be watched for with great care.

3. The need for intensive bacteriologic study before and during the treatment with antibiotic agents cannot be overemphasized.

4. The use of streptomycin and penicillin simultaneously at the beginning of treatment of an infectious disease is not recommended.

Cases 4 and 5 have previously been reported in greater detail in the *New England Journal of Medicine*.<sup>2</sup>

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## INEFFECTIVE USE OF STREPTOMYCIN IN RHEUMATOID ARTHRITIS

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AN infectious polyarthritis of rats, first described by Collier,<sup>1</sup> appears to be identical with or closely related to the rat disease shown by Findlay,<sup>2</sup> Mackenzie, MacCallum and Klieneberger<sup>3</sup> to be due to a pleuropneumonia-like organism. Sabin<sup>4</sup> described a proliferative polyarthritis of mice produced experimentally with a pleuropneumonia-like organism, and Preston<sup>5</sup> isolated a similar organism from spontaneous rat arthritis and was able to reproduce the disease in rats. The possibility that this polyarthritis of rats and mice might be a counterpart of human rheumatism stimulated studies<sup>6,7</sup> which at first indicated that pathogenic pleuropneumonia-like organisms could be obtained from exudates and tissues of patients with rheumatic fever. However, in further investigations this was disproved.<sup>7,12</sup>

In spite of such negative findings there remained the fact that Findlay, Mackenzie and MacCallum,<sup>4</sup> and, later, Sabin and Warren<sup>9</sup> found that certain gold compounds exert a curative effect on arthritis of rats and mice due to pleuropneumonia-like organisms. Since gold salts also appear to have a beneficial effect in human rheumatoid arthritis, it seemed possible that the experimentally produced disease of rodents might serve to screen compounds for possible effectiveness in rheumatoid arthritis.

A pleuropneumonia-like organism was isolated in this laboratory from a spontaneous joint infection in a laboratory rat. This animal showed a swollen right foreleg, particularly at the radiocarpal joint, and the initial culture was obtained by aspirating a drop of fluid from the joint and culturing in beef infusion broth enriched with 30% ascitic fluid. On incuba-

tion at 37° C. for 24 hours, this and subsequent cultures in the same medium showed marked turbidity, and after an additional 24 hours incubation the growth generally settled as a deposit of flakes in the bottom of the tube. Microscopically the culture showed either small gram-negative bacilli or gram-negative débris or both. Electron micrographs of the organism were presented from these laboratories by Weiss.<sup>13</sup>

The technique for reproducing arthritis in normal rats consisted in injecting 0.5 cc. of 24 hour ascitic fluid broth culture intravenously. During the 3rd, 4th and 5th days after injection, a progressive polyarthritis developed, in which there were fusiform swellings of the toes, and progressive swelling of leg joints, the skin over these areas becoming tight and glistening and red or purplish in color. Within a few days, many of the infected rats showed a hemorrhagic deposit and edema about the nose and sometimes a conjunctivitis. An occasional rat had neurologic symptoms. Animals infected as described and receiving no chemotherapy died, generally in about 2 or 3 weeks. Treatment with gold sodium thiomaleate (myochrysine) was quite generally effective as noted in an earlier publication.<sup>5</sup>

During the past 2 years, using myochrysine-treated rats as a standard for comparison, we have examined more than 65 compounds as to their effect against this type of arthritis. Among these was penicillin<sup>6</sup> which, like all the others, failed to compare at all favorably with the gold salt. However, when streptomycin was used a result superior to that obtained with the myochrysine was consistently observed.<sup>6</sup>

In the first experiment, 4 infected rats of about 100 gm. weight were treated with

streptomycin hypodermically, while 6 animals were retained as controls. Therapy was started about 1 hour following infection, and 3 doses of 1 mg. each were given 1st, 2nd and 3rd days, for a total of 9 doses. The 4 treated rats remained entirely free of symptoms, while 5 of the 6 controls developed pleuropneumonia infection. Two of these were dead in 5 days, before definite gross arthritis could appear, but the other 3 developed disabling joint involvement.

As recounted elsewhere,<sup>6</sup> this experiment was repeated with larger groups of animals and with almost identical results.

**CLINICAL USE OF STREPTOMYCIN.** The finding of a chemotherapeutic agent which appeared superior to gold salts in treatment of rat polyarthritis prompted experimental use of streptomycin in human rheumatoid arthritis. Sufficient drug was obtained for treatment of 5 patients through the offices of C. S. Keefer, M.D., Chairman of the Committee on Chemotherapeutic and Other Agents, National Research Council. Subsequently, treatment of 4 patients with higher dosage was attempted in order to reach a definite and final conclusion.

Patients were selected to represent both early and advanced types of rheumatoid arthritis but in each instance unmistakably active disease was present as indicated by the criteria established by a committee of the American Rheumatism Association.<sup>2</sup> The duration of disease from the initial attack of arthritis ranged from 7 months up to as long as 10 years, but in only 1 patient (E. W.) had there been almost continuous arthritis for a prolonged period of time. In the others the disease had been more or less intermittent, the current attacks being, with 2 exceptions, no longer than 12 months. The systemic symptoms of rheumatoid arthritis were present in all, and each patient had an elevated erythrocyte sedimentation rate. Ages ranged from 24 to 52 years, and there were 8 females and 1 male.

The disease activity was graded as either 2+ or 3+ in all instances on a scale in which 1+ indicates minor but

definite evidence of rheumatoid arthritis and 4+ the fulminating type of disease.

Roentgenographic evidence of disease in the involved joints varied from minor bone atrophy without other findings in the earliest case to narrowed joint spaces and evidence of destruction of articular surfaces in the most advanced case. Except for the elevation in sedimentation rate, laboratory examinations indicated only the commonly found secondary anemia so often seen in rheumatoid patients.

**DOSAGE.** The first 5 patients were given 10 gm. of streptomycin in either 5 or 6 days with single doses of 200 or 250 mg. injected intramuscularly at intervals of 3 hours. Blood concentrations of streptomycin were calculated for 2 of these patients with the paper disk-plate method using *Staph. aureus* as the test organism.<sup>10</sup> In 1 case, concentrations of 0.019, 0.012 and 0.004 mg. per cc. were obtained at the end of 1, 2 and 3 hours following a dose of 200 mg., while the other patient showed ascending concentrations following injection of the same amount, the readings being 0.012, 0.016 and 0.019 mg. per cc.

To complete the study it seemed desirable to treat other patients with large doses on the order of 4 gm. daily for 20 days. Only 1 of those selected was able to complete such a course. Two others developed toxic symptoms, later described, which limited their high dosage treatment to 6 days for a total of 25 gm. in 1 instance, and 7 days and 29 gm. in the other. After discontinuance of therapy and disappearance of toxic symptoms these patients were given an additional 2 gm. each, only to have evidence of intolerance return. The fourth patient was given the balance of streptomycin remaining on hand at the rate of 4 gm. daily for a total of 30.5 gm. The maximum blood concentration of streptomycin obtained in estimations on 2 patients was 0.231 mg. per cc. 1 hour after injection of 500 mg.

**RESULTS OF TREATMENT.** Careful joint evaluations were done on each patient before and after treatment and again at



TABLE 1.—ANALYSIS OF DATA  
Streptomycin (intramuscular)

Case	Age	Sex	Duration since first attack	Duration of current attack	Degree of disease activity	Daily dose (gm.)	Total dose (gm.)	Max. blood conc. (mg. per cc.)	Side effects	Clinical results				
										Immediate	Objective	Subjective	Sedimentation (mm. hr. Wintrobe)	Follow-up result
O. S.	24	F	4 yrs.	12 mos.	2+	1.6 (200 mg. q. 3 hrs.)	10 (in 6 days)	0.019	None	Not impr.	Not impr.	Mod. impr.	Before 14 After 25	Severe joint pain in 1 wk.
I. J.	38	F	7 mos.	7 mos.	2+	1.6 (200 mg. q. 3 hrs.)	10 (in 6 days)	0.019	None	Not impr.	Mod. impr.	Mod. impr.	15	Joint pain 3 days after discharge
L. M.	37	F	10 yrs.	3 yrs.	3+	2.0 (250 mg. q. 3 hrs.)	10 (in 5 days)	0.010	None	Not impr.	Mod. impr.	Mod. impr.	21	Subjective impr. for 1 mos.
V. B.	36	M	7 yrs.	12 mos.	2+	1.6 (200 mg. q. 3 hrs.)	10 (in 6 days)	0.013	None	Not impr.	Mod. impr.	Mod. impr.	39	Subjective impr. for 3 mos.
H. G.	25	F	2 yrs.	2 yrs.	2+	2.0 (250 mg. q. 3 hrs.)	10 (in 5 days)	..	Dizziness	Not impr.	Mod. impr.	Mod. impr.	28	Subjective impr. for 1 mos.
E. W.	40	F	6 yrs.	6 yrs.	2+	4.0 (500 mg. q. 3 hrs.)	80 (in 20 days)	0.231	Hypertrexia; nausea	Not impr.	SL impr.	SL impr.	38	Acute joints continued unchanged
F. M.	52	F	18 mos.	18 mos.	2+	4.0 (500 mg. q. 3 hrs.)	25 (in 6 days)	..	Hypertrexia; nausea; generalized skin eruption; purpura	Not impr.	Mod. impr.	Mod. impr.	33	SL impr. for 2 mos.
						2.0 (250 mg. q. 2 hrs.)	2 (in 1 day)							
L. O.	49	F	27 mos.	3 mos.	2+	4.0 (500 mg. q. 3 hrs.)	20 (in 7 days)	0.042	Hypertrexia; nausea; generalized skin eruption	Not impr.	SL impr.	SL impr.	32	Acute joints continued unchanged
						2.0 (500 mg. q. 3 hrs.)	2 (in 4 doses)							
H. J.	51	F	9 yrs.	3 mos.	3+	4.0 (500 mg. q. 3 hrs.)	30.5 (in 8 days)	..	Nausea; deafness; vertigo	Not impr.	SL impr.	SL impr.	30	Acute joints continued unchanged

longer intervals during the follow-up period. Notations were made without reference to earlier examinations in an effort to record unbiased opinion. In no case was there definite evidence of objective improvement. As is so often true with new remedies for arthritis, subjective improvement was quite general, and 3 patients claimed definite benefit for as long as 4 or 5 months following completion of treatment. It is interesting to note that those receiving the greatest amount of streptomycin seemed to improve the least. The erythrocyte sedimentation rate was not altered significantly by streptomycin.

**TOXIC EFFECTS.** Among the 5 patients given a daily dose of 1.6 or 2 gm. only 1 complained of what may have been evidence of intolerance to streptomycin. After isolated doses there was a transient dizziness which was brief in duration and appeared to be of little significance. However, side-effects were quite general among those given 4 gm. daily. Nausea was a complaint of all 4, and it was of such intensity as to interfere with food intake. Three patients developed hyperpyrexia with temperatures occasionally rising as high as 104° F., but usually ranging from normal to 102° F. In each instance, temperatures leveled off to normal when streptomycin was discontinued. One patient (E. W.) continued with daily fever to 102° F. throughout 20 days of treatment.

Two patients developed a generalized skin eruption at the end of 6 and 7 days of high dosage therapy, 1 having had a total of 25 gm. and the other 29 gm. A macular rash first appeared over the chest and progressed to cover the entire body

as a maculopapular eruption. In 1 of these cases purpuric spots appeared on the second day of the eruption. Streptomycin was stopped in both patients as soon as the skin lesions appeared and within 7 days all evidence of intolerance had disappeared. To prove that streptomycin was the provocative agent, both patients were again given the drug for a total second course of 2 gm. In both cases the rash was reproduced but with less intensity than on the first occasion.

One patient complained of deafness on the 7th day of treatment with 4 gm. daily. Streptomycin was stopped on the 8th day, at which time vertigo also was a complaint. There was prompt though incomplete recovery of hearing but the vertigo has persisted for 10 weeks at the time of writing this report.

**Summary and Conclusions.** 1. Polyarthritis of rats due to the pleuropneumonia-like organism isolated in these laboratories is not useful in screening drugs for possible effectiveness in human rheumatoid arthritis.

2. Effective treatment of this type of rat polyarthritis with streptomycin led to experimental use of the drug in 9 patients with rheumatoid arthritis. Total doses of 10 gm. given over a period of 5 or 6 days and larger total quantities ranging from 25 to 80 gm. given at a rate of 4 gm. daily did not appreciably alter the course of rheumatoid arthritis in the cases studied.

3. With daily doses of 4 gm. of streptomycin, side-effects were quite general. These consisted of nausea, hyperpyrexia, skin eruption, and deafness with vertigo.

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## SULFATHIAZOLE IN THE ABNORMAL HUMAN BILIARY TRACT\*

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KNOWLEDGE of the rôle chemotherapeutic agents play in diseases of the human gall bladder and bile ducts has been in a rather confused state. This prompted Zaslow, Counseller and Heilman<sup>16,17</sup> to study the problem with regard to the antibiotics, penicillin and streptomycin. These studies indicated that the agents were not excreted into the biliary tract in the presence of either mechanical obstruction of the bile duct, acute cholangitis or impaired hepatic function. It followed that these antibiotics were of little value under such circumstances in treating infections of the biliary tract. In addition, it also was observed that the antibiotics were not excreted through the wall of the gall bladder but reached the lumen through the bile flowing in the biliary tree. The uselessness of these drugs in treating local infection in the presence of acute obstructive cholecystitis was obvious. As a result of those studies, we decided to investigate the effectiveness of the sulfonamides. The present report deals with the excretion and concentration of sulfathiazole in the human gall bladder and bile ducts. A plan similar to that used in the previous investigation was followed.

**Review of Literature.** Carryer and Ivy<sup>3</sup> found high concentrations of sulfanilamide in dog's bile after oral administration of a single dose of 2 gm. Hubbard and Anderson<sup>6</sup> reported that sulfanilamide was regularly found in human bile drained from the bile ducts following oral ingestion of 2 gm. They also noted that a higher concentration of acetylated sulfanilamide appeared in the blood than in bile draining out of T tubes. Spink, Bergh

and Jermsta<sup>15</sup> also reported that a greater concentration of the acetylated forms of sulfanilamide and sulfapyridine was found in the blood of man than in the bile and observed that the liver concentrated sulfapyridine but not sulfanilamide. Bettman and Spier<sup>2</sup> found that the degree of concentration of sulfanilamide in the human gall bladder was directly influenced by the concentrating power of that organ as measured by the Graham-Cole test. More recently Shay and co-workers<sup>14</sup> reported that following oral administration of the drugs the concentration of sulfathiazole and sulfasuxidine in dog's bile was more than 2 times that in the blood, while the concentration of sulfaguandinine in the bile was the same as that in the blood. However, they observed that some of these sulfonamides were not excreted into the dog's gall bladder and raised the question of their usefulness in treating disease of the gall bladder in which the cystic duct is occluded. Lynn, Bergh and Spink<sup>8</sup> had previously arrived at a similar conclusion regarding the action of sulfanilamide, sulfathiazole and sulfadiazine in the dog.

The evidence as to the clinical usefulness of these agents, although infrequent, is rather confusing. Cleveland,<sup>5</sup> reporting a case in which he believed that sulfanilamide was instrumental in curing cholangitis following choledochoduodenostomy, stated that the drug was indicated in treatment of damage to the liver associated with cholangitis. Mancke, Plötner and Siede<sup>9</sup> reported that they successfully treated 6 patients who had acute cholangitis by the use of prontosil either orally

\* Estimations of sulfathiazole in bile were made in the Division of Biochemistry under the supervision of Dr. M. H. Power.

or parenterally administered. The dose was small, only 0.6 gm., 3 times a day. They noted, however, that there was no improvement in cases of chronic cholangitis. Rehfuß<sup>13</sup> stated that sulfonamides should be used in treatment of acute hepatitis and acute disease of the biliary tract, with the reservation that "when there is severe damage or mechanical obstruction, we can only hope to control temporarily the infection of the ducts in this way." Morrison reported that he was able to sterilize the biliary tracts of all patients who had streptococcal infection, but he did not name the associated condition in the biliary tree;<sup>11</sup> however, at a later date he added "provided there was no cystic duct obstruction in the dog or human."<sup>10</sup> He was unable to cure patients who were infected with *Escherichia coli*. Bazin<sup>1</sup> reported the case of a carrier of *Salmonella paratyphi* in which treatment with sulfanilamide was successful.

Contrary to the foregoing favorable reports, Spink, Bergh and Jermsta<sup>15</sup> could find no effect from sulfanilamide or sulfapyridine in the treatment of 2 patients whose bile ducts were infected with *E. coli*. Peterson, Deutsch and Finland,<sup>12</sup> although reporting favorably on the effect of sulfathiazole and sulfadiazine in treatment of acute hepatitis, noted only failure in 3 cases of cholangitis. Lembcke<sup>7</sup> reported failure in treating a typhoid carrier.

In general, when the sulfonamides were used in the treatment of infections of the biliary tract, any clinical improvement observed was attributed to the chemotherapeutic agents. Most often the occurrence of natural remission in the disease was disregarded. It appears that the usual assumption was that since the drugs were excreted in the bile of the normal dog and man, they were very likely also excreted into the obstructed and infected biliary tree.

The present investigation is reported in 2 parts: (1) sulfathiazole in the gall bladder; (2) sulfathiazole in hepatic bile.

1. SULFATHIAZOLE IN THE GALL BLADDER. *Method of Study.* Twenty-five patients

scheduled for cholecystectomy were selected. At a definite interval before operation each patient was given 3 gm. of sulfathiazole orally. This was taken after fasting and no food was eaten after the drug was administered. The time elapsing between ingestion of the drug and performance of cholecystectomy was noted. The level of sulfathiazole in the bile removed from the gall bladder was determined by the method described by Carrier and Osterberg.<sup>4</sup> Only the level of free sulfathiazole was determined. Notes were made as to the presence and position of stones in the gall bladder at the time of operation. The condition of the liver and biliary tree, as well as the function of the gall bladder as determined by the Graham-Cole test, were recorded.

**Results.** (Table 1.) Seven patients had non-functioning gall bladders which contained stones. The time intervals between ingestion of sulfathiazole and determination of its concentration in gall bladder bile varied from 2½ to 12 hours. In 4 cases no drug was found in the contents of the gall bladder; the cystic duct was obstructed by a stone in each case, 2 gall bladders were reported as hydropic and 1 showed microscopic evidence of acute inflammatory changes in the wall. The levels of sulfathiazole in the contents of the remaining 3 non-functioning gall bladders varied from 0.75 to 1.8 mg. per 100 cc.; the cystic ducts in these cases were patent.

There were 15 patients whose functioning gall bladders contained stones. The time elapsing from ingestion of sulfathiazole to determination of its concentration in gall bladder bile varied from 2 to 14 hours. In the gall bladder bile of 7 of these patients sulfathiazole was not found. In 6 of these 7 the cystic duct was obstructed by a stone at the time of operation; in the other patient, although the cystic duct was patent, drug was not found in bile from the gall bladder. This patient had marked obstructive jaundice; it is likely that no sulfathiazole was excreted by the liver. The findings in this case are explained in this report. The concentrations of drug in the bile of the remaining 8 patients who had functioning

gall bladders which contained stones varied from 0.31 to 2.7 mg. per 100 cc.

Three patients had no stones in the gall bladder at the time of operation. Sulfathiazole was not found in the bile of 1 patient who had obstructive jaundice at the time of operation; the concentrations of drug in the bile of the remaining 2 patients were 0.85 and 1.6 mg. per 100 cc., and the time intervals 5 hours and 3 hours, respectively.

peated at definite intervals, it is likely that higher concentrations would have been attained. It cannot be stated with any degree of certainty either that the drug is absorbed from the lumen of the gall bladder or that it is greatly concentrated in the gall bladder. The fact that sulfathiazole was present as long as 13 hours after oral administration at least suggests that it can remain in a non-contracting gall bladder for long intervals.

TABLE 1.—CONCENTRATION OF SULFATHIAZOLE IN GALL BLADDER BILE FOLLOWING ORAL ADMINISTRATION OF 3 GM.

Type of gall bladder	Concentration of free sulfathiazole (mg. per 100 cc.)	Time after ingestion (hrs.)	Obstruction cystic duct
Non-functioning (stones present)	0.85	2½	No
	0	3	Yes*
	0	3	Yes
	1.80	4	No
	0	10	Yes†
	0	12	Yes†
	0.75	12	No
	0.31	2	No
	0.94	2	No
	0	2½	Yes
Functioning (stones present)	0	2½	No‡
	0.70	2½	No
	0	3	Yes*
	0.45	3½	No
	1.88	5	No
	0	6	Yes
	0.85	4½	No
	0	10	Yes
	0	11	Yes
	0.71	12	No
	2.70	13	No
	0	14	Yes
	1.60	3	No
No stones	0.85	5	No
	0	14	No‡

\* Reported by pathologist as acute cholecystitis superimposed on chronic cholecystitis.

† Reported by pathologist as hydropic.

‡ Obstructive jaundice present.

**Comment.** It appears that the most important factors concerned with the appearance of sulfathiazole in the lumen of the gall bladder are the patency of the cystic duct and the ability of the liver to excrete the drug. In each case in which these factors were favorable the drug was recovered in bile from the gall bladder. While the concentrations were low, varying from 0.31 to 2.7 mg. per 100 cc. of bile, it must be remembered that only a single dose of 3 gm. was given orally. Had larger doses been given initially and re-

In addition, since in most instances the amount of sulfathiazole present was less than 1 mg. per 100 cc. of bile, it is likely that little concentration of the drug took place in the gall bladder.

It is also well to recall that in the 2 cases in which acute inflammation was found in the wall of the gall bladder no sulfathiazole was present in the lumen when the cystic duct was obstructed. This suggests that acute inflammation does not alter the mode of entrance of the drug.

## 2. SULFATHIAZOLE IN THE HEPATIC BILE.

*Method of Study.* Ten patients who had undergone choledochostomy and insertion of a T tube were selected for study. Between the 4th and 7th days after operation each patient was given 3 gm. of sulfathiazole orally. This was given only in the absence of nausea and abdominal distention and when the patient was taking fluids well by mouth. Specimens of bile were collected from the T tubes at intervals of 2 to 6 or more hours. The concentration of sulfa-

all studies of excretion were repeated at intervals for 2 weeks after operation in order to determine whether there was any change in the ability of the liver to excrete the drug.

**Results.** (Table 2.) The cases were divided into 2 groups as determined by the ability or inability to excrete the drug as indicated by results of the initial tests.

*Group 1.* Five patients failed to excrete the drug at the time of initial study. A

TABLE 2.—EXCRETION OF SULFATHIAZOLE IN HEPATIC BILE AFTER INGESTION OF 3 GM. OR INTRAPERITONEAL ADMINISTRATION OF 5 GM.

Case	Jaundice (duration present attack, days)	Liver function test* (sulfobromophthalein)		Preoperative serum bilirubin (mg. per 100 cc.)		Excretion of sulfathiazole	
		Grade	Postoperative day	Direct	Indirect	Mg. per 100 cc. (maximum)†	Postoperative day of test
1	0	0	Preop.	0		0	3
		4	4	1.8	0.5	1.53‡	9
		0	9	0			
2	0	1	4	..	..	0‡	4
						1.29‡	8
3	2	..	..	11.0	0.7	0§	
						0¶	5
						0.60¶	14
4	1	..	..	9.0	2.7	0§	
						1.72‡	14
5	7	2	3	3.5	0.5	0§	
						0.19¶	6
6	0	2	6	..	..	0.18‡	5
						0.34‡	7
7	3	0	14	6.3	2.1	0.44¶	3
						1.50‡	15
8	0	3	5	..	..	0.42‡	3
						1.22‡	9
9	0	..	..	0	0.8	1.55‡	4
						1.55‡	10
10	0	4	5	..	..	1.76‡	4
		0	7				

\* Grades 1 to 4 (1 is least) retention; Grade 0 is normal.

† Only the concentration of free drug was determined.

‡ Normal serum bilirubin concentration when test was made.

§ Intraperitoneal administration of drug.

¶ Serum bilirubin falling when test was made.

thiazole in the bile was determined by the method of Carryer and Osterberg. When jaundice was present, it was observed whether the jaundice was increasing or decreasing as indicated by the concentration of serum bilirubin. In most cases in which icterus was not present a sulfobromophthalein test for hepatic function was performed. In several cases in which 5 gm. of sulfathiazole were left in the abdominal cavity at operation, the concentration of sulfathiazole in the bile was determined 2, 4, 6 and 12 hours after operation. In a few cases

short résumé of the histories and pertinent laboratory studies is presented.

CASE 1. Several attacks of jaundice had occurred in preceding years, but none in the few months just before operation. All laboratory work, including a sulfobromophthalein test for hepatic function, gave negative results. At operation a gall bladder filled with stones was removed. The common duct was explored. While no stones were found, the bile was thick and inspissated. On the 3rd postoperative day

(day of operation is taken as the 1st) the patient failed to excrete sulfathiazole during a 6 hour period. A test for hepatic function performed on the 4th day showed retention of dye, Grade 4 (in which Grade 1 is least and Grade 4 most severe). The value for serum bilirubin at this time was 1.8 mg. per 100 cc. direct and 0.5 mg. indirect. The patient's course was uneventful; on the 9th postoperative day the patient excreted a maximum of 1.53 mg. of sulfathiazole per 100 cc. of bile and a test for hepatic function gave negative results.

We had expected this patient to excrete both test dye and sulfathiazole on the 4th and 3rd days, respectively; however, it appeared that either the operation or the anesthesia (nitrous oxide, oxygen, ether) or both had temporarily further impaired a liver which already had little reserve function as a result of previous icteric episodes. This impression is supported by the fact that the results of a test for hepatic function made before operation were negative, but results of a similar test performed on the 4th postoperative day indicated retention, Grade 4. The patient quickly recovered her ability to excrete both the test dye and sulfathiazole.

CASE 2. Repeated attacks of pain in the upper part of the abdomen, associated with jaundice and fever on a few occasions, had occurred in the 2 years before the patient's registration at the Mayo Clinic. All pre-operative laboratory tests gave negative results. At abdominal exploration no abnormality was found in either the gall bladder or bile ducts. Cholecystostomy and choledochostomy were performed. It was thought that the patient probably had had recurrent attacks of intrahepatic jaundice. On the 4th postoperative day the patient failed to excrete in the bile any sulfathiazole in a 24 hour period. A test for hepatic function revealed retention of dye, Grade 1. The concentration of serum bilirubin was normal. The patient had a chill on the 5th postoperative day, her oral temperature rose to 102° F. and she complained of pain in the right upper quadrant of the abdomen similar to that experienced on previous occasions when she had been icteric. The

symptoms rapidly subsided and no jaundice developed. On the 8th postoperative day another sulfathiazole test revealed that the patient excreted 1.29 mg. per 100 cc. of bile in a 2 hour specimen.

In Case 2, as in the preceding case, it appears that either the operation or the anesthesia or both had temporarily further impaired the function of a liver which already had little reserve.

CASE 3. Repeated attacks of biliary colic had occurred for many years. While undergoing study at the clinic, the patient had an attack of typical colic, followed by chills, oral temperature of 102° F. and jaundice. The value for serum bilirubin 2 days before operation was 11 mg. per 100 cc. direct and 0.7 mg. indirect. At operation the common bile duct was found to be greatly dilated; a stone was impacted in the lower end. Cholecystectomy, choledocholithotomy and choledochostomy were done. Five gm. of sulfathiazole were left in the abdominal cavity. Specimens of bile collected in a period of 6 hours contained none of the drug. On the 3rd postoperative day the value for serum bilirubin had decreased to 2.9 mg. per 100 cc. direct. The patient's general condition was satisfactory. On the 5th postoperative day, following oral administration of 3 gm. of sulfathiazole, no drug was found in the bile; however, when the test was repeated on the 14th day, a concentration of 0.6 mg. per 100 cc. was found.

This patient had active obstructive jaundice when the initial test was carried out. No sulfathiazole was excreted in bile at this time or on the 5th day. However, after most of the jaundice had disappeared, there was some excretion of the drug in the bile.

CASE 4. There was no previous history of disease of the gall bladder. However, on the day before operation the patient had an attack of pain in the right upper quadrant of the abdomen, followed by fever, jaundice and a rapidly developing perforation of the gall bladder. The concentration of serum bilirubin the day of operation was 9 mg. per 100 cc. direct and 2.7 mg. indirect. At operation bile was found free in the abdominal cavity. Cholecystectomy and choledochos-

tomy were done. No stone was found in the common duct at the time; it was thought inadvisable to explore too long because of the patient's poor condition. Five gm. of sulfathiazole were left in the abdominal cavity. There was no excretion of the drug in the bile in the first 10 hours after operation. The patient's condition steadily improved and the concentration of serum bilirubin gradually returned to normal. On the 14th postoperative day a concentration of 1.72 mg. of sulfathiazole per 100 cc. of bile was found after oral administration of the drug.

The same process as in Case 3 appears to have been active in Case 4.

CASE 5. Cholecystectomy and choledocholithotomy had been performed 1 year before the patient's admission at the clinic. Because of the large size of the duct and a persistent filling defect observed in the choledochogram, the T tube had been left in place for more than 3 months. The patient had been well following removal of the tube until a few days before readmission. At that time she experienced an attack of biliary colic followed by jaundice. The concentration of serum bilirubin 2 days before operation was 3.5 mg. per 100 cc. direct and 0.5 mg. indirect. At operation stones were not found in the common or hepatic ducts. The pancreas was normal. A T tube was left in the common duct. Three gm. of sulfathiazole had been given to the patient orally 1 hour before operation. None of the drug was excreted in the bile for 6 hours after operation. The postoperative course was uneventful. A test for hepatic function performed on the 3rd postoperative day revealed retention of dye, Grade 2. The concentration of serum bilirubin at that time was 1.1 mg. per 100 cc. direct and 0.9 mg. indirect. On the 6th postoperative day the patient excreted 0.19 mg. of sulfathiazole per 100 cc. of bile in a  $3\frac{1}{2}$  hour specimen obtained after the ingestion of 3 gm. of drug.

Case 5 seems to fall into the same category as Cases 3 and 4.

*Group 2.* Five patients excreted sulfathiazole in bile at the time initial tests were made.

CASE 6. Two attacks of jaundice had occurred, the most recent one a month previously. All preoperative studies gave negative results. At operation stones were not found in the common bile duct or gall bladder. The surgeon stated that hepatitis, Grade 2, was present. Cholecystectomy and choledochostomy were done. On the 3rd postoperative day the patient excreted 0.18 mg. of sulfathiazole per 100 cc. of bile in a 6 hour specimen obtained after oral administration of a dose of 3 gm. of drug. A test for hepatic function performed on the 5th postoperative day disclosed retention of dye, Grade 2. On the 7th postoperative day a concentration of 0.34 mg. of sulfathiazole per 100 cc. of bile was found on repetition of the test for excretion of drug.

Although this patient excreted sulfathiazole on both occasions, the value was low. This is compatible with the existence of the hepatitis found by the surgeon and with impairment of hepatic function as shown by results of the sulfobromophthalein test. It might very well have been that the previous attacks of jaundice were caused by hepatitis.

CASE 7. Attacks of colic in the right upper quadrant of the abdomen had occurred for 1 year. There had been no jaundice until several days before operation, when the patient had had an attack of colic followed by jaundice. The concentration of serum bilirubin the day before operation was 6.3 mg. per 100 cc. direct and 2.1 mg. indirect. At operation a carcinoma of the gall bladder which had invaded the liver was found. There were stones in the common duct and gall bladder. Cholecystectomy, partial hepatectomy, choledocholithotomy and choledochostomy were done. Following operation the value for serum bilirubin decreased to normal after the 1st week. Sulfathiazole was given orally on the 3rd postoperative day; as a result, 0.44 mg. of drug per 100 cc. of bile was found in a 6 hour specimen. The study was repeated on the 15th day. At that time a concentration of 1.5 mg. per 100 cc. was reached.

CASE 8.—Attacks of colic and jaundice had occurred 16 years and 1 year before admission at the clinic. There was no jaundice at the time of the present admis-



sion. At operation multiple stones were found both in the common bile duct and in the gall bladder. A test for excretion of sulfathiazole performed on the 3rd post-operative day showed a concentration of 0.42 mg. of drug per 100 cc. of bile in a 2 hour specimen. A test for hepatic function made on the 5th day disclosed retention of dye, Grade 3. A test for serum bilirubin gave negative results. On the 9th day administration of sulfathiazole resulted in the excretion of 1.22 mg. of drug per 100 cc. of bile in a 6 hour specimen. The results of a test for hepatic function were reported as negative at that time.

CASE 9. After cholecystectomy had been performed, many years before, the patient had had numerous attacks of colic, but no jaundice at any time. The preoperative concentration of serum bilirubin was normal. At operation many stones were found in the common duct. The duct was markedly dilated. A test for excretion of sulfathiazole made on the 4th day showed that 1.55 mg. of drug per 100 cc. of bile were excreted during a period of 6 hours. A similar test made on the 10th day gave similar results.

CASE 10. A history of jaundice and colic was elicited. At operation stones were not found in the common bile duct but many were found in the gall bladder. Cholecystectomy and choledochostomy were done. A test for excretion of sulfathiazole performed on the 5th postoperative day showed a value of 1.76 mg. of drug per 100 cc. of bile in a 4 hour specimen. A test for hepatic function made on the same day revealed retention of dye, Grade 4, but a similar test made 2 days later showed no retention.

**Comments.** Three of the 5 patients who excreted no sulfathiazole in bile when the initial study was made had obstructive jaundice which was either stationary or was not subsiding rapidly at the time of operation. When the jaundice started to subside after operation, sulfathiazole in greater or lesser amounts was found in the bile. Two patients who failed to excrete the drug did not have jaundice at the time of operation; however, the drug was excreted in large amounts 8 and 9 days later, respectively. It is suggested that the damage incidental to

anesthesia and operative manipulation was probably sufficient in these 2 cases to impair hepatic function.

The remaining 5 patients excreted variable amounts of the drug, as indicated by the results of initial tests. Only 1 patient (Case 7) was icteric at the time of operation and the icterus appeared to be subsiding. One patient (Case 6) who was thought to have hepatitis, confirmed by the occurrence of retention of dye, Grade 2, as shown by tests made 3 and 7 days post-operatively, failed to excrete more than 0.34 mg. of drug per 100 cc. of bile. These concentrations were definitely low. Four patients (Cases 7, 8, 9 and 10) each secreted more than 1 mg. of sulfathiazole per 100 cc. of bile in either initial or subsequent tests. Two patients (Cases 9 and 10) who did not have jaundice and whose tests for hepatic function gave negative results excreted, respectively, 1.55 mg. of sulfathiazole per 100 cc. of bile and 1.76 mg. at the time of initial examination.

From this study it appears that either active obstruction of the bile ducts or hepatic damage may hinder or prevent excretion of sulfathiazole in bile. When either is marked, none of the drug is excreted. However, as obstruction is overcome and hepatic function returns, as it will if damage is not great, more and more of the drug is excreted by the liver.

**Clinical Importance.** It is apparent that the cystic duct must be patent for sulfathiazole to reach the lumen of the gall bladder. Morrison observed the importance of this factor in treating infections of the gall bladder in both the lower animal and man. The roentgenologic findings as to the function of the gall bladder cannot be relied on to reveal whether the duct is patent at the time treatment is given, since a gall bladder which contains stones may become obstructed at any time. It follows, then, that any chemotherapeutic approach to treatment of chronic disease of the gall bladder is at best uncertain. In treatment of acute obstructive cholecystitis we can state more definitely that

the drug most likely would be of no local value.

Since sulfathiazole is not excreted in the bile during active obstruction of the biliary ducts, it is difficult to see how this drug can be effective in the treatment of cholangitis associated with obstructive jaundice. We seriously question the good results attributed to the drug under such circumstances. Rather, it would seem that the infection subsides spontaneously. The drug likely may prove of value in preventing spread of infection to the parenchyma of the liver. For sulfathiazole to be effective, a free flow of bile must be established either by external or internal drainage and the liver must not be so seriously damaged that it cannot excrete the drug.

While this study was concerned only with the excretion of sulfathiazole, a few preliminary studies in which sulfanilamide and sulfadiazine were used have shown similar results.

**Summary and Conclusions.** CONCERNING SULFATHIAZOLE IN THE GALL BLADDER. 1. Following oral administration of 3 gm. of sulfathiazole:

(a) No drug was found in bile from the gall bladder when the cystic duct was obstructed.

(b) The drug was present in bile from the gall bladder when the cystic duct was

patent and when the liver excreted it normally.

2. Sulfathiazole is likely to be of no value in the treatment of patients who have acute obstructive cholecystitis.

3. The usefulness of sulfathiazole in treatment of any given patient who has chronic cholecystitis with stones is uncertain.

4. Acute inflammation of the gall bladder does not alter the mode of entrance of the drug to its lumen.

CONCERNING SULFATHIAZOLE IN HEPATIC BILE. 1. After oral ingestion of 3 gm. of sulfathiazole or intraperitoneal administration of 5 gm., the drug is excreted in the hepatic bile of normal patients.

2. In the presence of obstructive jaundice the ability of the liver to excrete the drug is impaired.

3. The greater the degree of hepatic damage the less is the amount of drug excreted in the bile.

4. As the concentration of serum bilirubin approaches normal, more sulfathiazole is excreted in bile.

5. Sulfathiazole is likely to prove of no value in treatment of patients who have acute obstructive jaundice with cholangitis.

6. Free drainage of bile must be established if the drug is to be active.

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## REITER'S SYNDROME

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RENEWED interest has recently been stimulated in the study of Reiter's syndrome, a disease entity of unknown etiology whose classical manifestations are the triad of urethritis, arthritis and conjunctivitis. Since Reiter's original descriptive communication in 1916, less than 80 additional cases in 29 articles have been reported. These have appeared mainly in recent years from medical staffs of military installations where there were accumulations of large groups of young men whose age is apparently propitious to the disease.

Although the paucity of literature and general incognizance of the condition suggest the rarity of the syndrome, the observation of 12 cases in 2 years by a single observer refutes this contention and indicates the necessity for further awareness of the disease in diagnostic considerations. The propensity for exaggerated symptoms involving in 1 case 1 bodily system and in another a second, often simulating a diversity of other diseases, has obscured the diagnosis. Yet, since clinical inaccuracies engender misleading implications of therapy and prognosis, prompt recognition is important.

**HISTORICAL.** Attention was first called to the singular character of the disease by Reiter<sup>10</sup> in Germany during the first World War. He observed a soldier who, initially complaining of diarrhea, subsequently developed polyarthritis, purulent urethritis, conjunctivitis, mild cystitis and pustular lesions over the hips. Unable to ascribe specific cause to the complex and procuring no therapeutic success with the agents available to him, Reiter conceived of the syndrome as a new entity. Shortly thereafter 2 independent reports were made by Fiessinger<sup>5</sup> in France, and Macfie<sup>9</sup> in Africa.

Although sporadic reference to this curious disease continued in the foreign literature, the first American description appeared in 1942, when Bauer and Engleman<sup>1</sup> reported a series of 6 cases. In 1944, Lever and Crawford<sup>8</sup> contributed 2 more cases emphasizing the dire dermatologic complications that may result. Rosenblum<sup>11</sup> in 1945 reviewed 10 cases observed by him in a Naval Hospital. At the same time Hollander<sup>7</sup> and a group of investigators at an Army Medical Center reported a series of cases presenting a type of arthritis which they believed to be specific only for Reiter's syndrome. Colby,<sup>3</sup> and Sargent,<sup>12</sup> in separate publications, have more recently revealed the severity of complications involving the urinary tract. It is doubtful, however, whether in all these cases the patients actually had Reiter's disease, since in some the triad was not complete and in others the bacteriologic studies were not sufficient to exclude the possibility of a gonococcic infection.

The 12 cases selected in this series were those in which indisputable diagnosis could be made. In every instance the requisite specifications of the triad were met and meticulous clinical and laboratory study was performed to exclude all other clinical possibilities. So-called atypical cases are not recorded.

**CLINICAL PICTURE IN 12 CASES.** The 12 patients observed were males between the ages of 19 and 34. All reported the illness as the initial episode and such follow-up studies as have been possible fail to disclose recurrence. Only 1 patient gave a family history of joint disease. Previous episodes of gonorrhea were established in 6 cases, only 1 of which, however, preceded the onset of Reiter's disease by less than 6 months. History

of non-specific urethritis was recorded by 2 patients; in both instances no complications had ensued and symptoms had subsided promptly. In 1 case recurrent attacks of conjunctivitis without other manifestations were noted for 2 years prior to the syndrome.

The initial symptom in 9 cases was urethritis. Conjunctivitis occurred simultaneously with urethral discharge in 1 patient and mild diarrhea heralded the onset of disease in another. In only 1 instance did the arthritis appear in precedence to the other signs. The time required for the complete syndrome to develop varied from 2 to 30 days; usually the clinical picture was complete within the first 10 days of illness.

The urethral discharge usually began as a glairy mucoid exudate which later became frankly purulent. Repeated smears and cultures were negative for gonococci in every case and at no time could any specific organism be isolated. The urethritis, in most instances, cleared up in less than 2 weeks, but in several cases persisted as long as 6 weeks. Remission of the discharge with subsequent recurrence was observed in 4 patients. Dysuria and frequency accompanied the urethritis in 50% of the cases, while the rest showed asymptomatic discharge. Three patients developed subsequent prostatitis and 1 severe hemorrhagic cystitis. In no case in this series was involvement of the upper urinary tract observed. Circinate lesions of the penis developed in 3 cases. Superficial ulceration of the glans in 1 patient progressed into severe balanoposthitis, but in others the balanitis regressed spontaneously within a week. Only 1 patient demonstrated skin lesions suggestive of keratoderma blennorrhagica. In this case a keratotic eruption appeared on the dorsal surfaces of both hands followed by a herpetiform rash on the palmar surfaces of the feet. The vesicles on the right foot enlarged, coalesced and ruptured, provoking a shallow ulcer. Later a hyperkeratotic lesion developed on the tip of the right third toe.

Purulent conjunctivitis was present in every case and in all but 1 its appearance preceded the onset of arthritis. Generally, the conjunctivitis was of mild or moderate severity with hyperemia, edema and yellow mucopurulent discharge. Superficial keratitis was observed in 1 patient. Usually the severe inflammatory reaction subsided in 3 or 4 days, but in 1 case persisted for 2 weeks. Conjunctival scrapings were consistently negative for inclusion bodies. Cultures of the discharge were either sterile or showed growth of *Staph. albus*.

The cardinal feature of the syndrome in every case was the arthritic phase. Invariably there was a sudden elevation of temperature accompanied by an acute onset of severe to moderate joint pain. The affected joints were red, hot, swollen and tender. Although in 2 cases only a single joint was involved, generally the arthritis was polyarticular and of a migratory type simulating acute rheumatic arthritis. Most commonly the knees and ankles were affected. Less frequently involved were the wrists, hips and interphalangeal finger joints. In 1 unusual case the temporomandibular joint was acutely inflamed. Hydroarthrosis of the knee was present in 6 cases. Roentgenographic studies of the affected joints ordinarily revealed only evidence of soft tissue swelling and the presence of joint fluid. In 2 cases suggestive osteoporosis of the bone ends appeared, although this was not clearly defined. Joint aspirations, carried out in 5 cases, revealed serous fluid with low protein content, 10,000 to 20,000 white cells per c.mm. with a preponderance of polymorphonuclear cells. Cultures of synovial fluid were persistently sterile.

Supplementary laboratory examinations in this survey corresponded more or less to the studies in previous reports. Serologic reactions of the blood were negative in every instance. Electrocardiographic tracings were insignificant in 5 studies. During the acute phase of the illness, leukocytosis ranging from 10,000 to 22,000 per c.mm. was found and a coincidental

elevation of the sedimentation rate was observed. Blood cultures in 2 patients yielded no growth. Because of its unreliability, the complement fixation test for gonorrhea was not employed, although in every case cultures for Neisserian organisms were taken of the exudates from the conjunctiva and urethra and, where possible, of joint fluid. Urine cultures were done on all patients, only 3 of which were positive; 2 for *Staph. albus* and 1 for *E. coli*. Pyuria was present in every case at the outset, but cleared up in at least half the cases before the disease terminated. No animal inoculations were done.

The clinical course of the syndrome appeared to follow a fairly constant pattern. Generally the essential triad was complete within 1 month and the acute phase would reach its zenith in 6 to 8 weeks. Temperature elevations were not pronounced and usually of short duration; in no case accompanied by chill. Following the acute stage, in most cases, involved joints remained swollen, stiff and painful. In only 2 cases was there exacerbation of the acute inflammatory process after initial remission. Total duration of symptoms is presumably subject to considerable variation; entirely accurate follow-up in every case has not been possible. In no case, however, was a patient fully recovered in less than 3 months, and 3 patients were still hospitalized after 4 months of illness.

**Comment.** This curious syndrome with its standard pattern and its variegated clinical complications presents an etiologic problem. Although a variety of causative agents have been suggested, conclusive evidence is lacking to substantiate the position of any as the responsible factor. Several investigators have proposed dysentery organisms, others streptococci and coliform organisms, and Reiter himself, an atypical spirochete. Recently Dienes and Smith<sup>4</sup> isolated a pleuropneumonia-like organism which is apparently associated with genito-urinary infections and may have significant relationship to the

Reiter complex. Such bacteria, however, were not discovered in our cases.

This disease would seem to be confined to young men, although 1 dubious case in a female was described by Lever and Crawford.<sup>8</sup> Epidemiology remains obscure, and the present consensus rejects the notions of contagion or nutritional deficiency. In a consideration of geographic distribution, Vallee<sup>13</sup> finds that cases have been reported from western Europe, the United States, and the Pacific Islands.

Pathologic examination of the synovia of the involved joints has been carried out in only 3 cases. Hollander<sup>7</sup> and his associates, who performed arthrotomy and biopsy in 1 patient, report that the synovial membrane was congested and presented a reddish purple appearance. No gross thickening was observed, but several areas of white fibrinous material were present on the surface of the synovial membrane. Microscopic examination revealed a severe inflammatory reaction which was limited to the superficial synovial layers. Their report says the synovial membrane was thrown into large club-like projections in which abundant capillaries were dilated. Each projection was distended by a heavy lymphocyte infiltrate mixed with a few plasma cells and neutrophils. There was no evidence of exudate. The intima was found to be several cells deep. There were no new capillaries and the marked hyperemia consisted of dilatation of the preëxisting capillaries. These findings corroborate the pathologic changes observed in earlier reports by Bauer and Engleman,<sup>1</sup> and by Wepler.<sup>14</sup>

Specific therapy for Reiter's syndrome is unknown. Penicillin, sulfonamides, arsenicals, salicylates and fever therapy have all been recently employed. The great variety of medications tried indicates the inefficiency of each. Effective therapeutic efforts have thus far been limited only to analgesics and palliative measures directed at symptomatic relief.

Despite the unavailability of definite

treatment, prognosis in general is good. No death directly ascribable to the disease has been reported. Although recurrences of the syndrome are known to occur months and even years after the original episode, each attack is generally self-limited in its course without residual structural or functional disorder of the affected systems. In rare instances permanent articular and ocular damage has been reported. Complicating skin lesions are uncommon and invariably are characteristic of keratosis blennorrhagica. Urologic complications are usually of a mild transient nature.

Diagnostic accuracy demands differentiation of Reiter's syndrome from gonorrhea. Clinically the gonorrheal syndrome presents a more severe reaction with chills and high fever. It frequently causes permanent joint damage, but usually responds to chemotherapy. Nevertheless, the only

indisputable evidence in differential diagnosis is determined by meticulous bacteriologic studies, since in Reiter's disease gonococci are never found.

**Summary.** 1. Reiter's syndrome is an unusual disease encountered in young males characterized by urethritis, conjunctivitis and migratory arthritis. Skin lesions are occasionally noted; these appear as either keratosis blennorrhagica or balanitis circinata.

2. The etiology of the disease is obscure. No definitive therapy is available.

3. The course of the disease is self-limited, never terminating, however, in less than 3 months. Recurrences are not unusual and may occur years after the initial episode.

4. The disease is perhaps not as rare as has been supposed, since the 12 cases here presented were seen in 2 years by a single observer.

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## A STUDY OF HEPATIC FUNCTION IN ACQUIRED MALARIA\*

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EXPERIENCED medical men have long noted the apparent transitory hepatitis that so frequently is associated with acquired malaria. Many texts designate a "malarial hepatitis" as a complication to be carefully observed. The term "malarial hepatitis" may be confusing, but the hepatic dysfunction it describes is evident to the physician.

Our study originated in a general hospital early in 1943 because we were impressed by the frequent occurrence of abnormal liver function tests in malarial cases. A search of the literature at that time failed to reveal much concrete evidence substantiating such a clinical occurrence. Most texts of tropical medicine discuss this phase of malaria from a clinical point of view only. During the progress of this study several publications bearing on this problem have occurred. Kopp and Solomon<sup>3</sup> in January 1943, in studying induced malaria, concluded that a transitory effect of diminished hepatic function occurred in 9 patients they observed. Mirsky, Von Brecht and Williams<sup>4</sup> in January 1944 reported a study of 10 patients with acquired malaria and the relationship of serology to cephalin flocculation and concluded that the Kahns were negative and the Hanger tests positive in the absence of therapy.

Kern and Norris<sup>2</sup> in November 1944 studied 100 proven *P. vivax* and *P. falciparum* cases. They concluded: "The outstanding fact to which attention is directed in this report is that demonstrable involvement of the liver occurs in the majority of all cases of malaria and in all stages of the disease, including the earliest

acute attack. Furthermore, the incidence is far greater than is commonly realized."

Fredericks and Hoffbauer<sup>1</sup> in June 1945 studied 31 cases of induced malaria in syphilitics and found an increase in serum bilirubin during or after therapy in 14 of 31 cases. There was an increase in the urinary excretion of urobilinogen in 12 of 13 cases tested. There was a positive Hanger test and a retention of bromsulphalein in all cases tested.

Read, Kaplan, Becker and Boyd,<sup>5</sup> in reporting on 300 cases of neurosyphilis treated with therapeutic malaria, discussed the occurrence of malarial hepatitis and pointed out that this complication in mosquito-inoculated cases attests, at least in some instances, to a more specific toxic effect of malaria on the liver than merely by the accidental transmission of an hepatotoxic agent with a blood inoculation.

The laboratory tests reported here represent a careful evaluation in about 250 cases studied in 1943 and 1944. The observations have been repeatedly spot checked since that time both in this country and in New Guinea and the Philippines representing several thousand cases. We believe they accurately represent the picture during the acute phase of infection studied.

**Methods.** Cases were selected carefully to include nothing but *Plasmodium vivax* parasitemia. All cases had smears of peripheral blood examined on entrance to the hospital. As soon as the parasites were demonstrated, therapy with quinacrine hydrochloride was started. Schedules were arranged so that when the patient became afebrile the liver function tests were im-

\* The bromsulphalein used in this study was supplied through the courtesy of Hynson, Westcott & Dunning.

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mediately done. Usually this occurred within 2 or 3 days of hospital entrance. Atabrine was prescribed as follows: 2 tablets (3 gr.) every 6 hours for 5 doses, then 1 tablet t.i.d. for 5 days. All of the function tests were done while atabrine was being given for demonstrated parasitemia. All cases of clinical liver disease such as epidemic hepatitis, amebic hepatitis, cirrhosis, etc., were eliminated from the series. The laboratory tests were done by the same personnel under the same conditions. All abnormal tests were rechecked as soon as practical.

mal was taken to be, for cholesterol, 150 to 250 mg. per 100 cc. serum and for the esters 50 to 70% of the total. Hippuric acid (oral method of Quick, p. 76) was regarded normal at 3 to 6 gm. Prothrombin time, determined after the method of Page and Russel (*J. Lab. and Clin. Med.*, 26, 1366, 1941), was regarded normal up to 23 seconds.

One hundred patients had a series of liver function tests which included the cephalin cholesterol flocculation test, prothrombin time, bromsulphalein, icteric index, hippuric acid, total protein, albu-

TABLE 1.—COMPARISON OF LIVER FUNCTION TESTS IN 2 DIFFERENT GROUPS OF PATIENTS

Test	Group 1		Group 2		Total fraction (all cases)	Average % positive
	Fraction (Fig. 1)	% positive	Fraction (Fig. 2)	% positive		
Bromsulphalein . . . .	16/100	16	25/80	31	41/180	23
Icteric index . . . . .	31/100	31	26/84	31	57/184	31
Hippuric acid . . . . .	38/100	38	39/98	40	77/198	39
Prothrombin . . . . .	30/100	30	27/84	32	57/184	31

In the fraction under each column the numerator represents the number of abnormal tests and the denominator the total tests done.

TABLE 2.—CORRELATION OF POSITIVE REACTIONS FOR EACH TEST WITH THE POSITIVE REACTIONS GIVEN BY ALL OTHER TESTS

	A	B	C	D	E	F	No other positive
A—pos. Hanger . . . . .	64	23/36	9/14	21/33	24/37	14/22	11/17
B—pos. prothrombin . . . .	23/77	30	5/17	12/40	10/33	4/13	1/3
C—pos. bromsulphalein . . .	10/62	5/31	16	9/56	7/44	3/19	1/6
D—pos. icteric index . . . .	21/68	12/39	8/26	31	9/29	6/19	2/6
E—pos. hippuric acid . . . .	24/63	10/26	6/16	9/24	38	8/21	6/16
F—pos. protein . . . . .	14/61	4/17	3/13	6/26	8/35	23	3/13

Numerator of fraction denotes number, denominator denotes percentage, of positive reactions of test indicated by letter at head of column.

The methods used in this study (except for prothrombin time) may all be found in Simmons & Gentzkow.<sup>6</sup> Pages are noted in parentheses for each specific test. For total protein (method of Army Medical School, page 221) the normal range was taken to be 5.3 to 8.5 gm. per 100 cc. of serum; for globulin, 1.3 to 3 gm. per 100 cc. serum and the normal A/G ratio was taken to be 1.3 to 2.5 to 1. Cephalin-cholesterol flocculation, done after the method of Hanger (p. 77), was regarded as normal up to 2+; icteric index (method of Meulengracht and Bernheim, p. 213) normal up to 11; bromsulphalein (5 mg. per kg. intravenously, p. 73) normal up to 6% retention. For cholesterol and cholesterol esters (method of Schoenheimer and Sperry, n. 211), the nor-

min, globulin and A/G ratio. For the sake of simplicity all of the protein tests have been gathered into 1 group so that we may consider each patient to have had 6 different tests.

Figure 1 is a summary of all the tests in this group and their relationship to each other. It might be pointed out that about one-third of all patients tested showed 3 tests abnormal and about two-thirds showed 2 or more abnormal tests.

A variable number of patients not included in Figure 1 had other tests in addition to the above, or the same tests, that can be used as a check on the evalua-



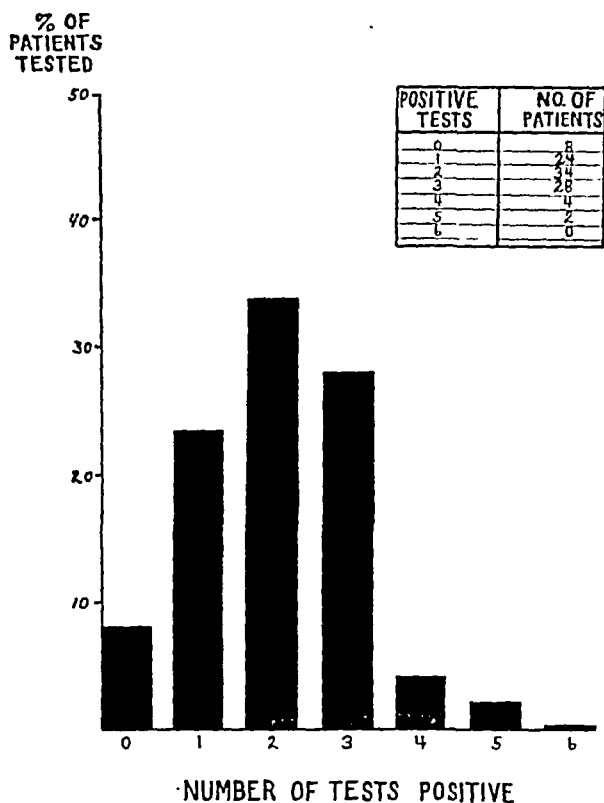


FIG. 1.—COMPARATIVE RESULTS IN PATIENTS OF GROUP 1.

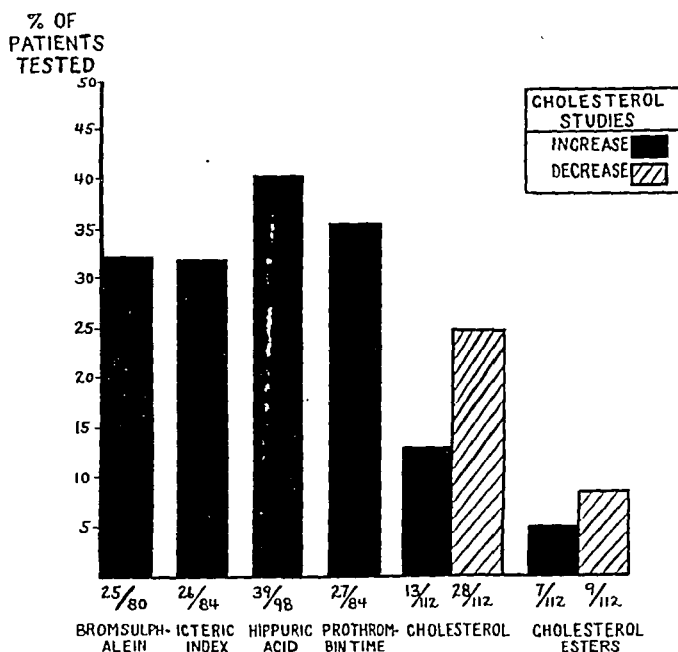


FIG. 2.—Comparative results in patients of Group 2. In the fraction under each column the numerator represents the number of abnormal tests and the denominator the total tests done, i. e., bromsulphalein, 80 tests performed of which 25 were abnormal.

tion of these 100 cases. These are shown in Figure 2.

It can be seen from Table 1 that the comparison between the 2 groups was nearly identical except for the bromsulphalein. We have no obvious explanation for this variant.

An additional 112 patients were examined under the same conditions for cholesterol—cholesterol esters; of these, 28 (25%) showed an increase in total cholesterol, 13 (12%) a decrease in total cholesterol, 9 (8%) an increase in cholesterol esters and 7 (6%) a decrease in cholesterol esters.

In analyzing the results, it is of interest to note that about three-fourths of the positive tests were correspondingly matched by other positive tests as demonstrated in Table 2.

**Summary.** One hundred cases of acute acquired malaria under atabrine therapy received a series of liver function tests. In addition, another group of about 150 patients were tested with random liver function tests and the results of both groups compared.

Our personal observations in the United States, New Guinea and the Philippines, continuing these studies but not herein

reported, have supported the conclusions of this report in every way.

Although long range follow-up studies were impossible, under our conditions, it is our clinical opinion that the hepatic dysfunction demonstrated is transitory. It rarely, if ever, leaves permanent liver damage with the possible exception of cases where previously diseased livers existed and in which extension of the process may occur. This may result in more rapid development of the chronic cirrhotic liver occasionally seen from the tropics.

**Conclusions.** 1. Approximately one-third of all acute acquired malaria cases under atabrine therapy are shown to have demonstrable hepatic dysfunction as evidenced by standard liver function tests.

2. Less specific tests, such as the cephalin flocculation test, are positive (3+ to 4+) in about two-thirds of the cases.

3. None of the liver function tests used was accurate when used alone as an index of hepatic dysfunction.

4. A significant number of clinical cases of acquired benign tertian malaria under atabrine therapy show definite evidence of hepatic dysfunction.

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# PROTEIN DEPLETION AND HEPATIC FUNCTION IN THE DOG

## RATIONALE OF METHIONINE IN THERAPY

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It is now generally accepted that protein depletion renders the liver more susceptible to damage by hepatotoxic agents and that methionine and cystine are the specific protein factors which will protect susceptible animals.<sup>7,9,10,15,16,17</sup> The mechanism of this protective action is not clear, but it has been shown that the liver of protein depleted dogs is not only depleted of protein but is relatively more deficient in sulfur (S) than nitrogen (N) (increase in N/S), and that this ratio is restored toward normal by methionine or cystine.<sup>17</sup> This protective action is probably independent of the lipotropic action of methionine because choline alone has been found without protective effect against chloroform liver damage in dogs<sup>17</sup> and rats.<sup>6</sup> However, a simultaneous choline deficiency with fatty liver unquestionably renders the liver even more susceptible to damage.

It is known that a small supplement of methionine or cystine will spare the N of body protein stores in dogs on a very low protein diet<sup>18</sup> or greatly increase the biologic value of diets quantitatively or qualitatively,<sup>13</sup> inadequate in protein. But it is not generally recognized that the N sparing effect of a methionine supplement becomes negligible when the casein content is increased.

Expecting protein depletion to result in impaired liver function, we sought to study the effects of simple protein depletion and of methionine supplementation on hepatic function using a modification of the bilirubin clearance test of Von Bergmann and

Eilbott.<sup>23</sup> At the same time because of controversial reports of the therapeutic value of methionine in liver injury and protein deficiency states, we have made some observations on the N sparing effect of methionine when added to diets of varying protein content.

**Methods.** The dogs observed in the experiments of Table 1 were healthy mongrels on (1) a diet of mixed table scraps (kennel diet) which maintains weight and keeps them in good condition; (2) a very low protein diet containing sucrose 72.2%, Crisco 14.9%, Mazola oil 6.5%, cod-liver oil 1.4%, yeast powder (Fleischmann's Type 200-B) 0.7%, powdered liver extract (Lilly, H 8083) 0.7%, Wesson salt mixture 4.6%, calcium phosphate 4.6%. The diet was fed at a level to provide 70 calories per kilo body weight daily and was supplemented with 400 mg. choline chloride and 25 mg. of nicotinic acid daily. The dogs of Table 2 were maintained on the low protein, high fat diet of Hough and Freeman<sup>11</sup> which contains no choline except that which may be present in the yeast used.

The dogs of Table 3 were maintained on the very low protein diet described above with replacement of an approximately isocaloric portion of the diet by commercial casein in the indicated amounts. When the urinary N excretion became fairly constant, the daily supplement of 1 gm. of dimethionine was started. The bilirubin clearance of Tables 1 and 2 were carried out according to Von Bergmann and Eilbott with modifications.<sup>23</sup> Bilirubin (Eastman Kodak) was given intravenously in solution prepared by dissolving 3 mg. of bilirubin

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TABLE 1.—BILIRUBIN CLEARANCE UNAFFECTED BY PROTEIN DEPLETION

Normal Dogs

Dog No.	Dietary regime	Plasma protein level (gm.%)	Plasma bilirubin retention (%)
1	4 days 20 gm. casein daily after low protein diet	5.20	17.9
2	Salmon bread	7.10	16.7
3	Kennel diet	6.82	16.8
4	Kennel diet	6.23	14.1
5	Kennel diet	6.21	22.4*
6	Kennel diet	..	18.9
7	Kennel diet	6.05	22.8†
8	Kennel diet	6.59	20.0
9	Kennel diet	6.37	15.3†
9	Kennel diet	6.53	26.7‡
10	Beef liver 150 gm. per day plus low protein diet	5.75	19.4

Protein Depleted Dogs

1	10 day fast—9 wk. non-protein diet	4.70	16.1
3	7 day fast—7 wk. non-protein diet	4.84	19.3
7	4 day fast—7 wk. non-protein diet	5.05	18.4
9	10 day fast—9 wk. non-protein diet	4.67	18.0
11	7 day fast—7 wk. non-protein diet	4.23	19.0
12	4 day fast—7 wk. non-protein diet	4.94	20.7

\* After 72 hours fast.

† After 48 hours fast.

‡ After 10 day fast.

TABLE 2.—BILIRUBIN CLEARANCE ON CHOLINE DEFICIENT, LOW PROTEIN DIET

Weeks on diet

Dog No.	2		4		5.5		6.5		9	
	P.P. level (gm. %)	Bil. ret. (%)	P.P. level (gm. %)	Bil. ret. (%)	P.P. level (gm. %)	Bil. ret. (%)	P.P. level (gm. %)	Bil. ret. (%)	P.P. level (gm. %)	Bil. ret. (%)
3	5.21	19.8	..	..	..	..	..	..	4.58	33.4
4	5.71	16.2	4.93	30.2	5.18	37.2	4.97	45.0	..	..
8	5.44	19.9	..	..	..	..	..	..	5.07	46.7
9	5.61	32.4	..	..	5.08	35.8	4.82	32.4	..	..

TABLE 3.—NITROGEN SPARING ACTION OF DL-METHIONINE ON HIGH AND ON LOW N INTAKE\*

Dog 12 (wt. 11.7 kilos)—high protein intake (12.7 gm. N per Periods 1 and 2; 13.6 gm. N per Period 3 through 5)

Period 48 hrs.	1	2	Basal diet	3	4	5	6
T N urine	8.18	7.48	+ dl-Methionine	7.12	7.43	9.18	..
% urea-NH <sub>3</sub> N	89.40	90.00	1 gm. daily	92.20	90.70	89.40	..

Dog. 12 (wt. 11.4 kilos)—moderate protein intake (3.46 gm. N per period)

Period 48 hrs.	1	2	Basal diet	3	4	5	6
T. N. urine	3.53	3.27	+ dl-Methionine	2.09	1.95	1.90	..
% urea-NH <sub>3</sub> N	77.60	76.80	1 gm. daily	63.00	70.10	63.90	..

Dog. 12 (wt. 10.5 kilos)—very low protein intake (0.66 gm. N per period)

Period 48 hrs.	1	2	Basal diet	3	4	5	6
T N urine	2.29	2.18	+ dl-Methionine	1.51	1.18	1.29	1.18
% urea-NH <sub>3</sub> N	75.10	70.30	1 gm. daily	60.70	61.50	52.00	51.10

Dog. 13 (wt. 11.4 kilos)—high protein intake (14.1 to 14.2 gm. N per period)

Period 48 hrs.	1	2	Basal diet	3	4	5	6
T. N. urine	9.16	9.42	+ dl-Methionine	9.60	10.27	10.78	11.94
% urea-NH <sub>3</sub> N	92.20	94.20	1 gm. daily	93.90	88.80	92.70	90.50

Dog 13 (wt. 11.7 kilos)—moderate protein intake (3.98 gm. N per Period 1 and 2; 4.19 gm. N per Period 3 through 6)

Period 48 hrs.	1	2	Basal diet	3	4	5	6
T N urine	3.83	3.52	+ dl-Methionine	2.71	2.06	2.42	2.45
% urea-NH <sub>3</sub> N	78.70	82.80	1 gm. daily	77.60	72.30	71.80	72.70

\* N intake does not include 0.19 gm. N per period from methionine N.

per kilo body weight in 20 to 30 cc. of 1% sodium carbonate solution. No untoward reactions were produced. After exactly 5 minutes and 60 minutes had elapsed from the time of injection, samples of blood were drawn from the opposite external jugular vein and mixed with 1.4% sodium oxalate solution as anticoagulant. After centrifugation, aliquots of the clear plasma were treated according to the method of Malloy and Evelyn<sup>14</sup> for the determination of bilirubin. Color intensity was read in a Klett photoelectric colorimeter with a 54 filter. Lipemic or hemolyzed samples of plasma were rejected. The bilirubin retention figures in Tables 1 and 2 represent the per cent of bilirubin concentration present at 60 minutes in comparison with the 5 minute value as 100%.

Plasma protein concentrations and total urinary nitrogen determinations were made by macro-Kjeldahl. Urea-ammonia nitrogen was estimated by aëration and titration after urease treatment.

**Results and Discussion.** There were only insignificant changes in bilirubin clearance in the dog with protein depletion resulting from 8 to 10 weeks maintenance on a very low protein diet presumably adequate in calories and vitamins including choline (Table 1). In 2 unrecorded experiments in such protein depleted dogs, the addition of methionine to the diet several days before and intravenous injection immediately before the bilirubin clearance test failed to reduce the bilirubin clearance values below the normal values obtained without methionine. Furthermore in several animals, determination of prothrombin time by the method of Quick<sup>20</sup> showed no measurable change resulting from protein depletion of this duration. In the protein depleted dog there is thus a striking disparity between increased susceptibility to damage by hepatotoxic agents and continued ability to clear the blood of bilirubin, or to form prothrombin. This is at variance with reports<sup>5,11,12,24</sup> claiming rapidly developing impairment of liver function with protein depletion. The composition of the diets used in these cited experiments was such that the impaired hepatic function

reported to result from protein depletion *per se* may indeed have been the result of choline deficiency. In addition the dogs in many of these experiments rapidly became partially or almost totally anorexic and suffered large weight losses. The combined effects of protein depletion, choline deficiency and inanition cannot be ascribed solely to protein depletion. In fact, several of the animals cited in Table 1 show that prolonged fasting alone may be associated with decreased clearance of bilirubin from the plasma. Table 2 shows how the complication of choline deficiency resulting from the high fat, low protein diet of Hough and Freeman<sup>11</sup> produces early impairment of bilirubin clearance and indicates that choline deficiency is an added liability which may be superimposed on and complicate simple protein deficiency.

Current interest in the possible application of methionine and cystine to therapy has led to conflicting claims of its value. The best clinical results have been reported<sup>1,4,22</sup> in the treatment of hepatic injury resulting from exposure to chemical poisons and in the therapy of cirrhosis of the liver. The value of methionine in the treatment of infectious hepatitis is difficult to assess from reports<sup>19,21,25</sup> in which treatment may have been started too late to be of decisive value, or in which methionine was superimposed on a diet already containing considerable methionine in the form of dietary protein.

Table 3 contains evidence that a methionine supplement has little or no significant continued N sparing effect when the diet already contains large amounts of protein of good methionine content. In contrast to this is the distinct N sparing effect of methionine when added to a diet of moderate or very low protein content (Dogs 12 and 13). Wherever methionine supplementation spares N it does so at the expense of the urea-ammonia N fraction.

On the basis of these experimental findings it appears that methionine supplementation of diets already containing

large amounts of methionine and cystine in food protein may be unwarranted and even wasteful. By the same token, where digestion and absorption of such a high protein dietary are unimpaired, it seems unreasonable to expect any "supernormal" protective action from large supplements of methionine. Indeed Drill and Loomis<sup>2</sup> have been unable to demonstrate any "superprotection" against carbon tetrachloride liver damage when methionine is added to high casein diets.

To avoid possible untoward effects of great methionine overdosage,<sup>3</sup> it seems desirable to limit the total daily methionine intake to an amount equivalent to 1 to 1.5 gm. (per kilo body weight) of the best dietary protein. Using whole egg protein with 1.5% S as a basis for calculation, a 70 kilo man would require the equivalent of 4.9 to 7.4 gm. of methionine per day. On another basis, assuming a daily N loss of 10 to 20 gm. per day and a daily S loss of 0.63 to 1.25 gm. ( $N/S = 16$ ), then approximately 3 to 6 gm. of methionine should be adequate to replace the daily total S loss. The recently formulated minimal protein requirement for healthy normal males<sup>25</sup> would place the minimum intake level even lower.

The therapeutic use of methionine appears indicated: (1) as early as possible and continuously in any case of acute hepatic disease particularly toxic hepatitis, especially where the status of protein

nutrition is difficult to assess, and when during illness the dietary protein intake is poor or negligible; (2) where protein depletion is known to exist; (3) where the diet protein intake is suboptimal quantitatively by choice, or through inability to ingest, digest and absorb large amounts of good food protein; (4) where the diet protein intake is suboptimal qualitatively as a result of restriction to those proteins comparatively low in S content.

**Summary.** 1. Evidence is presented that simple protein depletion uncomplicated by choline deficiency produces no significant change in the ability of the dog to clear injected bilirubin from the blood. This is in distinct contrast to the greatly increased susceptibility of the protein depleted dog to hepatotoxic agents such as chloroform.

2. A high fat, low protein diet deficient in choline is associated with early impairment of ability to clear injected bilirubin from the blood.

3. The N sparing acting of methionine supplements in the dog varies with the total methionine content of a protein dietary in the dog. Maximal effect is observed where the protein intake is relatively low. Virtually no continued effect is seen where the diet already contains large amounts of methionine as protein.

The implications of these observations for the therapeutic use of methionine are indicated.

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# PERSISTENT FAMILIAL (NON-SPECIFIC) SEROLOGIC FLOCCULATION REACTIONS FOR SYPHILIS SUGGESTING AN HEREDITARY MECHANISM\*

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Is there such an entity as persistent, familial, non-specific reaction to a serologic test for syphilis? The existence of non-specific positive reactions is now generally accepted. In recent comprehensive reviews by Beerman<sup>2</sup> and Davis<sup>6</sup> a variety of causes are recorded. The rôle played by immunizations and intervening infections in producing transient positive serologic reactions in persons known to have been previously negative receives considerable attention. Beerman notes that recently there have been occasional reports of familial non-specific positives consequent to an infectious disease. Neither Beerman nor Davis, however, record any report of "idiopathic" false positive tests persisting in several members of a family. Stokes, Beerman and Ingraham<sup>13</sup> do not include in that portion of their text which deals with non-specific positives any instance of such an observation. Stokes, however, has expressed himself as follows: "Why should there not be such a thing as familial false positive reactivity, and why indeed should it not even have a gene distribution in association with blood types?"<sup>12</sup>

The mechanism of the production of a non-specific positive remains undetermined. Malloy and Kahn<sup>8</sup> stated that "it appears that the difference between non-syphilitic and syphilitic serum is one of degree rather than kind; that it is quantitative rather than qualitative." A similar conclusion was reached by Barnett, Jones and Kulcher.<sup>1</sup> Mohr and his associates,<sup>9</sup>

however, believe that normal reagin differs qualitatively from that of syphilitic serum. They present records of 9 individuals who were thought to give non-specific positive reactions, and from the study of these cases they feel that normal reagin may at times be present in sufficient concentration to give non-specific positives. The difference of opinion expressed in these 2 views is a fundamental consideration in any approach to the problem of how these reactions occur.

Familial occurrences of non-specific positive reactions, transient in duration and associated with acute infections, have been reported. Zugar and Moffat<sup>14</sup> record observations obtained on 3 brothers who had afebrile upper respiratory infections. Positive Kahn tests were obtained on the serum of each one, but their mother's serum was negative. One month later the reaction was negative in each instance. Lindau<sup>7</sup> reports the data on a family of 6. Both parents and 2 of the 4 children showed non-specific reactions to the Kahn and Wassermann tests following attacks of bronchitis. Within a short time, however, all the positive reactions became negative. Smith<sup>11</sup> studied 2 brothers whose serologic reactions to the Wassermann and sigma tests were positive following mumps. The sera of the parents gave negative reactions. One of the boys died of encephalitis due to mumps; the other one had a negative serologic reaction to both tests 4 months after the first determination. The cases cited by Mohr

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and his associations do not include any observation of a familial non-specific positive. The majority of their cases showed a transient false positive reaction. In 1 instance the positive reaction persisted for 6 months but further observations were not recorded.

The query at the beginning of this report was prompted by observations continued over a 2 year period on the members of a family. During this period the sera of several members showed a persistently positive reaction to 1 type of test and the reactions were felt to be non-specific. In addition to the finding of a familial incidence of a persisting non-specific positive reaction, some data were obtained which suggest the possible existence of an hereditary mechanism by which the non-specific positive factor was transmitted from 1 parent to several of her children.

**Family Study.** In February 1944, V. F., a 35 year old white female of Italian birth and 4 to 5 months pregnant, was seen in the prenatal clinic of the Lankenau Hospital. The routine prenatal serologic tests for syphilis showed a positive Kline test but a negative complement fixation reaction. A repetition of the serologic study 2 weeks later yielded identical results, and the patient was referred to the syphilis clinic.

The past history of the patient was not particularly helpful in evaluating her condition. There had been 4 previous pregnancies. The first 3 resulted in normal, full-term deliveries, but the fourth terminated by miscarriage at the 3rd month. The patient had been in the United States for about 20 years. There was no history of any treatment for syphilis. The only previous serious illness had been malaria at the age of 15 while she was still in Italy. The physical examination was not remarkable except for carious teeth. There was no evidence of congenital syphilis. Although it was not felt that a definite diagnosis had been established, it was considered advisable to begin treatment because of the pregnancy and its duration. From March 13, 1944, through June 27, 1944, the patient received weekly injections of nearsphenamine, maximum dose 0.45 gm., except for 2 weeks when she did not attend clinic. A living, normal, full-term female infant

was delivered on June 29, 1944. Subsequently the mother received rather irregular treatment during the next year.

Soon after the patient was first seen in the syphilis clinic an investigation of the family was done as a routine procedure. Considerable interest was aroused by the fact that the serum of each of the other 3 children gave a positive reaction to the Kline test, but, like their mother, a negative complement fixation reaction. Neonatal serologic studies on the child born in June 1944 resulted in negative results by both tests. Similar negative observations on the serum of the father were reported when he was studied later in the year. The results of all the routine examinations on the sera of the various members of the family are summarized in Table 1. For clarification a specimen of serum from each member of the family was tested at the Laboratory of the Graduate Hospital by quantitative serologic tests developed by Boerner and Lukens.<sup>4,5</sup> Flocculation and fixation of complement were studied. Multiple examinations were performed subsequently and the results are tabulated in Table 2. On the first examination the sera of the mother and the 3 older children showed very low units of complement fixation, values within normal range, but units of flocculation in each instance were sufficiently high to be accepted as definitely positive. Subsequently these results were duplicated twice on each of these 4 persons. The results of the second study on the serum of James F. were not a significant deviation, as the serum was still in the doubtful group according to the classification of Boerner.<sup>3</sup> In this classification  $2\frac{1}{2}$  units of fixation of complement are required for positivity, and 1 flocculation unit is required for positivity. The serum of the father showed no flocculation or fixation of complement when tested by the methods of Boerner and Lukens. The serum of the youngest child, Jean F., also gave negative results by this method when she was 11 months old.

A study of Table 1 shows consistency in the pattern obtained by the routine serologic tests on the sera of the mother and the 3 older children, as seen in the first and also the subsequent examinations. In none of the studies was there any evidence of reaction to the complement fixation test, but there was always some reaction to the Kline

test. The quantitative aspects are better illustrated by the methods of Boerner and Lukens. Incidentally, none of the 3 older children showed any evidence of congenital syphilis. The repeatedly negative results

obtained by both routine tests on the serum of the father contrast with the observations on these others. If the family is grouped according to these results, the father and the youngest child appear to form one group,

TABLE 1.—RESULTS OBSERVED WITH BOERNER-LUKENS SIMPLIFIED COMPLEMENT FIXATION TEST AND KLINE DIAGNOSTIC TEST

	B. F. Father Born 1900 Type O Rh Pos.	V. F. Mother Born 1909 Type A Rh Pos.	James Born 1925 Type A Rh Pos.	Josephine Born 1929 Type A Rh Pos.	Gloria Born 1933 Type A Rh Pos.	Jean Born 6/29/44 Type O Rh Pos.
February 1944	...	C.F. Neg. Kline +3				
February 1944	...	C.F. Neg. Kline +4				
March 1944	...	...	Wass. Neg. Kline +2	Wass. Neg. Kline +2	Wass. Neg. Kline +2	
June 1944	...	...	...	...	...	Wass. Neg. Kline Neg.
August 1944	...	C.F. Q.N.S. Kline +2				
November 1944	Wass. Neg. Kline Neg.					
November 1945	Wass. Neg. Kline Neg.					
February 1946	Wass. Neg. Kline Neg.	C.F. Neg. Kline +1	...	Wass. Neg. Kline +2	Wass. Neg. Kline +1	

All tests performed in the routine serologic laboratory of the Lankenau Hospital, Philadelphia.

TABLE 2.—BOERNER'S GROUPING AND CLASSIFICATION BASED ON FLOCCULATION AND FIXATION OF COMPLEMENT UNITS (BOERNER-LUKENS METHODS)

	B. F. Father	V. F. Mother	James	Josephine	Gloria	Jean
November 1944	...	Fix. Comp. $\frac{1}{2}$ Floc. 8 Class 5 Group 2				
December 1944	...	...	...	Fix. Comp. $\frac{1}{2}$ Floc. 4 Class 5 Group 2	Fix. Comp. $\frac{1}{2}$ Floc. 4 Class 5 Group 2	
January 1945	...	...	Fix. Comp. $\frac{1}{2}$ Floc. 8 Class 5 Group 2			
April 1945	...	Fix. Comp. 0 Floc. 4 Class 5 Group 2	Fix. Comp. $1\frac{1}{2}$ Floc. 1 Class 7 Group 2			
May 1945	...	...	...	...	...	Fix. Comp. 0 Floc. 0 Class 1 Group 1
July 1945	...	...	...	Fix. Comp. $\frac{1}{2}$ Floc. 8 Class 5 Group 2	Fix. Comp. 0 Floc. 8 Class 5 Group 2	
August 1945	...	...	Fix. Comp. 1 Floc. 4 Class 5 Group 2			
November 1945	Fix. Comp. $\frac{1}{2}$ Floc. 0 Class 1 Group 1					
February 1946	...	Fix. Comp. $\frac{1}{2}$ Floc. 8 Class 5 Group 2	...	Fix. Comp. 1 Floc. 8 Class 5 Group 2	Fix. Comp. 1 Floc. 8 Class 5 Group 2	

All tests performed in the laboratory of the Graduate Hospital, Philadelphia.

while the mother and the 3 older children form a second.

Efforts to study further the mother and her own family for evidence of syphilis were unrewarding. No other members of her family were here in the United States. She had little knowledge of the medical histories of her family, but she had never known of the administration of intravenous therapy to any of them while she was in Italy. One previous record of a serologic test for syphilis on the mother was obtained. This was in 1933, when a Wassermann test had been performed at another hospital, presumably before the birth of the third child. This was reported as negative. There was no record of the performance of a Kline or any other flocculation test at that time.

Neurath of the Department of Biochemistry, Duke University School of Medicine. When tested by his method of globulin fractionation<sup>10</sup> the sera of the mother and Gloria gave non-specific positive reactions. The test on the serum of Josephine, however, showed an inconclusive result. A second examination of the serum of the mother gave a similar result to that first obtained. The close grouping of 11 of 12 examinations in Class 5 would seem to be more than a coincidence. The single exception is still in Group 2, the doubtful class according to Boerner's classification.

During all this study there was no history of intercurrent infection in the members of the family or of any immunizations. The impression was strengthened that we were

Parents			
Father		Mother	
Age 46		Age 37	
Type O		Type A	
Rh positive		Rh positive	
C.F.* negative		C.F.* negative	
Floc. negative		Floc. positive	
Children			
↓			
James	Josephine	Gloria	Jean
Age 18	Age 17	Age 12	Age 2
Type A	Type A	Type A	Type O
Rh positive	Rh positive	Rh positive	Rh positive
C.F.* negative	C.F.* negative	C.F.* negative	C.F.* negative
Floc. positive	Floc. positive	Floc. positive	Floc. negative

\* C.F. = Complement fixation test.

A study of the blood groups was conducted on the entire family. The father and the youngest child were found to be in Group O while the mother and the 3 older children were in Group A. This division correlated exactly with the division of the family according to serologic tests for syphilis. The study of the Rh types, however, did not show a correlation, as all were Rh positive.

An analysis of Table 2 gives some interesting figures. Twelve examinations were done by the method of Boerner and Lukens on the sera of the mother and the 3 older children. Of these 12, 11 gave results which fell in Class 5, Group 2, according to the classification of Boerner, which offers 13 possible classifications.

Further confirmation of our assumption that the serologic reaction of the mother and 3 of the children were non-specific positive was obtained through tests done by Dr. Hans

dealing with an hereditary factor which caused a persistent, non-specific false positive reaction to flocculation tests for syphilis. The correlation of the blood groups with the serologic reactions seemed to relate this factor with a known hereditary phenomenon. The serologic reaction and blood groups of the entire family are summarized above.

**Comment.** Apparently no previous reports on this subject have recorded persistence of non-specific positive reactions for a 2 year period. Non-specific positive reactions seem to be related to extrinsic causes, such as infections or immunizations. The rare familial incidence reported previously have all been attributed to infections. The family whose study is being reported here showed no evidence of syphilis, and they had experienced

neither recent infections nor immunizations. The pattern of the positive serologic reactions is interesting in that only the flocculation tests were positive. A possible mechanism of hereditary transmission of the factor responsible for the non-specific positive reactions is suggested by the correlation of the blood groupings and the serologic reactions. The exact nature of this factor is not apparent from the present study.

It is unfortunate that the inaccessibility of the mother's family prevented further investigation in that direction. Any future offspring of the 3 children involved would furnish an opportunity to extend the hereditary study.

This investigation further emphasizes the importance of a prolonged serologic study and clinical evaluation of all cases

in which there is any doubt whatever concerning the existence of syphilis. Furthermore the clinical evaluation should in some cases be extended to the entire family.

**Summary.** The 6 members of an Italian family were studied for 2 years. Of the 6, 4 showed a persistently positive flocculation reaction to serologic tests for syphilis although there was no evidence of syphilis in any one of them. The reactions were regarded as biologic false positives. The correlation of the blood groupings with the serologic reactions suggested an hereditary mechanism as a possible explanation of the existence of the observed serologic phenomena. No further information regarding the exact nature of the factor responsible was obtained.

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# SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD OCCURRING IN IDENTICAL TWINS\*

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DESPITE the fact that there exists a satisfactory treatment for pernicious anemia and its neural complications, many features of these 2 conditions remain unexplained. Among these is the significance of inheritance as an etiologic factor.

While pernicious anemia seems to have an heredo-familial incidence and even gastric achlorhydria has been shown to occur in families,<sup>14</sup> very few cases of nervous system involvement with heredo-familial tendencies have been recorded. S. A. Kinnier Wilson<sup>16</sup> remarked, "The curious feature of these and other genealogies marked by transmission of Addisonian anemia is the absolute rarity with which the nervous syndrome makes an appearance. Among all the 199 cases from the National Hospital, heredity seemed to play no part, and not 1 of the kind has been personally observed."

In 1912, Willson<sup>15</sup> described a woman who died at the age of 43 with pernicious anemia and subacute combined degeneration. Her sister died of "tabes with anemia" and her maternal aunt died of pernicious anemia. Hurst<sup>4</sup> (1924) found a man with the nervous disease and anemia whose father, brother, paternal uncle and paternal grandfather had died of pernicious anemia. He later<sup>5</sup> reported a man with subacute combined degeneration whose paternal grandfather had pernicious anemia, and a woman with the cord disease whose mother had pernicious anemia. Maclachlan and Kline<sup>8</sup> traced a family tree through 5 generations in which there were 4 cases living with pernicious anemia, 7 living with secondary anemia, and 13 who had died of "anemia." In the third gen-

eration of this family there were 4 cases with possible nervous system involvement. Dorst<sup>2</sup> studied a family through 3 generations. One woman died at the age of 46 with both pernicious anemia and subacute combined degeneration. She had 3 daughters who died of pernicious anemia and subacute combined degeneration and 1 son who died of pernicious anemia. Liepelt<sup>7</sup> described pernicious anemia and spinal cord involvement in a mother and daughter. Johannessohn<sup>6</sup> and Tscherning<sup>12</sup> also reported briefly on the familial incidence of subacute combined degeneration.

Ungley and Suzman<sup>13</sup> reported a family in which 2 brothers died of subacute combined degeneration, 1 brother had pernicious anemia and 1 sister died of pernicious anemia. The sister had a daughter who died with subacute combined degeneration. They also described 2 sisters, 1 of whom had died of pernicious anemia and the other was then under treatment for subacute combined degeneration. Witts<sup>17</sup> reported on 2 sisters who had died of pernicious anemia. They had a healthy sister who had 2 daughters, 1 with pernicious anemia and the other with both pernicious anemia and subacute combined degeneration. In a study of the interrelation of pernicious and idiopathic anemias, Heath<sup>3</sup> referred to a family in which 3 sisters had pernicious anemia and subacute combined degeneration. Another sister died at 35 with what was "presumably pernicious anemia."

Ranson and Reback<sup>10</sup> gave an extensive report of a young man who had severe pernicious anemia with diffuse involve-

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ment of the nervous system and who recovered with liver therapy. This man's mother died of pernicious anemia and subacute combined degeneration and his paternal uncle also had both the anemia and spinal cord involvement.

Despite Wilson's skepticism as to the heredo-familial basis of subacute combined degeneration, the above reports would seem to suggest that such an etiologic factor might exist. To add to this data, we wish to record our observations on identical twins who developed the syndrome of posterolateral sclerosis with gastric achlorhydria and who both responded satisfactorily to the administration of liver extract.

**Report of Cases. Family History.** Nothing is known about the maternal grandparents of our patients. The paternal grandfather died in 1905 at the age of 75 from unknown causes. The paternal grandmother is still living in her 90's. There was no history of anemia or nervous system disease in any of the uncles or aunts. The father of the twins died in 1937 at the age of 83. The cause of his death was not accurately known. Their mother died in 1901 at the age of 40 from bronchopneumonia. The first born child was a sister who lived only 3 months. She died of a "leaking heart." Another older sister died at the age of 54, in 1941, because of complications related to an abdominal "growth."

Both of our patients are married. C. W. has 2 daughters (22 and 21 years old) both of whom are well. F. W.'s marriage has been without issue.

**CASE 1.** C. W., a white male, born May 22, 1890, began to notice "numbness and tingling" in his fingers and toes in the mornings, but were said to have disappeared after several months. In October 1938, the "numbness and tingling" returned and his physician noted some signs of incoördination in his lower extremities. His blood count was "normal" at this time.

In August 1939, the patient had a left inguinal herniorrhaphy at the Philadelphia Naval Hospital. In October 1939, the patient began to notice more unsteadiness of his gait. He staggered at times and found it harder to walk at night. He was considerably fatigued and fell asleep readily. He

had episodes of spontaneous crying. Because of these symptoms he reentered the Naval Hospital where the following observations were made: The general *physical examination* showed multiple small lipomata of the skin of the extremities and body, but was otherwise unimportant.

The *neurologic examination* showed the cranial nerves to be intact. The patient's gait was ataxic and he walked with a wide base. The Romberg test was positive. There was some dyssynergia and dysdiadokokinesia of all extremities. There was impairment of performance of skilled acts with his fingers. Muscle power, tone and volume were not disturbed. Touch seemed to be impaired in both feet. Position sense was lost in the toes. Vibration sense seemed to be intact, although later examination showed some impairment in the feet. Pain sensation was preserved throughout. Later on during his stay in the hospital, stroking the soles of both feet had painful cutting and burning qualities. The deep reflexes and periosteal reflexes in the upper extremities were equally hyperactive. The patellar and Achilles reflexes were absent. The lower abdominal reflexes were absent. No pathologic reflexes were noted.

The patient showed some mild confusion at times, was mentally dull, and poorly cooperative. He showed no emotional disturbances and no memory defects at any time.

Blood counts (Nov. 15, 1939): red blood cells, 4,360,000; hemoglobin, 14 gm. (84%); white blood cell count, 6200 (polymorphonuclears 65%, lymphocytes 27%, monocytes 8%). All other blood counts were relatively the same. Red blood cells were reported as normal in size and shape. The hematocrit on November 16 was 37 and on November 28 was 40.

The urinalyses were essentially negative. The blood Kahn tests were negative. A chest roentgenogram showed some emphysema of the pulmonary bases. The electrocardiogram revealed a moderate left axis deviation.

Gastric analysis with histamine on November 26 showed absence of free hydrochloric acid.

The cerebrospinal fluid showed protein, 20 mg. %; sugar, 68 mg. %; negative Kahn, colloidal gold of all zeros, and 1 to 2 cells. The cerebrospinal fluid was under normal

pressure and the Queckenstedt test was negative.

The patient was started on liver therapy in December 1939. He improved slowly but steadily. In the early weeks of his hospitalization, he had become weaker, was scarcely able to walk, and was finally confined to bed; but by the end of December he was able to walk with assistance. When discharged from the hospital in June 1940, he walked without assistance although the neurologic examination showed little change. He continued liver therapy at home and by January 1941 was able to return to "flagging" on the railroad. By October 1945 he was able to return to his original job as a brakeman, which he has held to date.

A neurologic examination on April 7, 1946, by one of us (G. S.) showed the following: The cranial nerves were intact. The patient's gait was steady but there was a little instability noted on turning. In the Romberg test slight swaying was still present. There was a little ataxia on the heel-to-knee test bilaterally. Pain, touch, temperature, vibration and position sense were intact throughout. All of the deep and superficial reflexes were hyperactive throughout with a transient ankle clonus on the right side. The abdominal reflexes were present. A right Hoffman sign was the only abnormal reflex noted, although plantar flexion was absent on the left side.

The patient is still receiving "1 cc. of crude liver extract" intramuscularly each week and takes 10 drops of HCl before meals.

CASE 2. F. W., the identical twin brother of C. W., was admitted to the Neurological Section of the University of Pennsylvania Hospital on Oct. 3, 1944. For 4 years the patient had been complaining of "trembling" of his hands, especially the right. He began to have tingling sensations in his fingers and feet in August 1944. His gait became unsteady. He had noticed no increased difficulty in getting around in the dark.

The general physical examination was negative except for the presence of multiple subcutaneous lipomata on the body and the extremities and an unsatisfactorily repaired right inguinal hernia.

The neurologic examination on admission to the hospital revealed the following: The cranial nerves were intact. The patient's

gait was unsteady and he walked with a wide base. The Romberg test was positive. There was a slight tremor at rest of both hands, more on the right side. There was no dysmetria, but an action tremor developed on doing the finger-to-nose test. There was definite ataxia on doing the heel-to-knee test bilaterally. Muscle power was reduced in both lower extremities and in the right upper extremity. Muscle tone and volume were normal. Pain, temperature and touch were unimpaired. Vibration sense and position sense were impaired in both lower extremities. The deep and superficial reflexes were increased bilaterally in the upper extremities. The patellar and ankle reflexes were decreased. The abdominal reflexes were present. There were no abnormal reflexes.

Blood count (Oct. 12, 1944): 4,000,000 red blood cells, with 78% hemoglobin (color index 0.9); white blood cells, 10,400 (85% polymorphonuclears, 11% lymphocytes, 4% monocytes). Repeated blood counts showed nothing unusual in the appearance of the erythrocytes. The patient developed a pneumonia while in the hospital. After recovery the red blood cell count was 3,500,000 with a hemoglobin of 75% (C.I. 1.1).

Blood urea nitrogen was 18 mg. %. Fast-ing blood sugar was 62 mg. %. Urinalyses were repeatedly negative. Several blood Kolmer and Kline tests were negative.

Gastric analysis with histamine showed absence of free hydrochloric acid.

The cerebrospinal fluid was under normal pressure and the Queckenstedt test was negative. The protein was 41 mg. % and the serology was negative, as was the colloidal mastic test.

Roentgenogram of the vertebral column showed moderate thoracic scoliosis and some minor uncertain bony changes.

Two small subcutaneous nodules were removed for biopsy. Microscopic examination identified them as lipomata.

Liver therapy was started on the patient after he recovered from his pneumonia. He was given 3 cc. of Lederle's Liver Concentrate (15 U.S.P. units/cc.) 3 times a week. This was continued after discharge from the hospital and was increased to 3 cc. daily from February to April 1945. Since then it has been decreased until he is now taking 3 cc. twice a week.

The patient has shown progressive im-

provement. Some clinical evidence of nervous system disease still persists. Examination on May 20, 1946, showed the gait to be slightly unsteady (spastic-ataxic). This was more evident on turning and was increased with both eyes closed. The Romberg test was positive. Slight dysdiadokokinesia in the upper extremities and ataxia in the heel-to-knee tests were noted. Muscle power, tone and volume seemed good. Position and vibration sense were still a bit impaired in both lower extremities. Pain, touch and temperature perceptions were intact. The deep reflexes were increased in the upper extremities. The ankle jerks were absent. Knee jerks were present but fatigued easily. Hoffman signs were present bilaterally. Babinski's sign was not noted.

This man has returned to his work and does not find his remaining nervous system dysfunctions at all incapacitating.

**Discussion.** Before any genetic interpretations were made, it seemed advisable to establish the monozygosity of our patients beyond reasonable doubt. While there is no absolute method to determine this, Rife<sup>11</sup> has listed a number of criteria which may establish the zygosity of twins. These are: (1) the nature of the fetal membrane, (2) sex similarity, (3) physical resemblance, (4) blood types and subgroups, and (5) finger and palm prints. We could obtain no data as to the presence of monochorionic or dichorionic fetal membranes in our patients. They were of the same sex and their physical appearance was so identical that we often misidentified them. Their resemblance to each other in many physical details as outlined by Fischer<sup>1</sup> was so close as to leave little doubt of their similarity in this respect. Also of interest was the fact that they both had multiple subcutaneous tumors (lipomata), many of these occurring in relatively identical places on the body and of about the same size. Their father had similar nodules under his skin.

Blood studies were graciously done for us by Dr. Neva Abelson of the Philadelphia Serum Exchange at the Children's Hospital, Philadelphia. The twins' blood showed identical reactions. Both belonged to Group A1. The erythrocytes of both

men reacted as follows: Anti-A1 positive; anti-N positive; anti-M positive; anti-Rho positive; anti-Rh' positive; anti-Rh" negative; anti-Hr' positive.

Dr. David C. Rife, of Ohio State University, kindly studied the finger and palm prints of our 2 patients. He reported,<sup>9</sup> "The homolateral similarities are greater than the bilateral similarities of either. Each has a pattern in the thenar area in the left palm, while neither right palm shows a pattern in this area. The total ridge counts of the finger tips agree extremely well, F. W. having 91 and C. W. 92. This is close, even for twins. . . . the similarities are so striking that I feel reasonably certain that the twins must be identical."

On the basis of these criteria, we feel justified in concluding that our patients are really identical twins and are monozygotic.

Our patients did not show anemia or hyperchromic macrocytosis of the erythrocytes at any time. The clinical neurologic picture was that seen in posterolateral sclerosis. It is now well known that the neural symptoms of pernicious anemia may precede the hemic change. Under such circumstances the diagnosis depends on the clinical neurologic picture, negative laboratory and clinical studies implicating other known etiologic agents, the absence of free hydrochloric acid in the stomach after the subcutaneous administration of histamine and, finally, favorable therapeutic response to the parenteral administration of liver extract. Our patients fulfilled all of these criteria and we have concluded that the nervous system disease in these men was of the pernicious anemic type despite the lack of characteristic blood changes.

Certainly no final conclusion as to the hereditary basis of posterolateral sclerosis of pernicious anemia can be reached from our observations of this single set of identical twins. Yet we do feel that our cases added to those already recorded in the literature seriously suggest such a possible etiologic factor. Monozygotic twins are



genetically and physically more alike than other siblings or indeed any other 2 people. A non-infectious, non-contagious disease process occurring in one first and not long afterward in the other of a set of mon-oval twins certainly strongly suggests a possible common inherent basis for the disease process. Then when this disease is found to occur in ordinary siblings and other family relationships, the common inherent factor of the twins assumes hereditary features.

Genetic interpretation of posterolateral sclerosis is made more difficult by the many gaps in our knowledge of the causative factors and pathogenesis of the disease itself, and of the etiologic relationship of the condition to pernicious anemia. The idea that posterolateral sclerosis represents a toxi-infectious degeneration of the nervous system because of the absence of free hydrochloric acid in the stomach is no longer tenable. The old idea that the neural process is related to the anemia alone has long since been discarded. Most authorities today view the neural and hemic pathologic processes as a conditioned deficiency disease. Yet the etiologic relationship of pernicious anemia and subacute combined degeneration of the spinal cord still remains obscure. For instance, we do not know if the factor responsible for the integrity of hemopoiesis is the same as the factor responsible for the prevention of the development of status spongiosus in the nervous system so characteristic of posterolateral sclerosis. There may be 2 (or more) separate substances contained in the one therapeutic agent—liver extract. A definite chemical substance, folic acid, as a possible precise factor in the deficiency syndrome called pernicious anemia is only now being investigated. To date, we have seen no reports on the effect of this substance on the neural syndrome.

If different chemical substances are found and proven for the prevention of the hemic syndrome of pernicious anemia

and for the prevention of the neural process of posterolateral sclerosis, the genetic problem might relate directly to these substances and their point of formation or use. Such a finding might well explain the greater incidence of the familial occurrence of pernicious anemia as Wilson so readily noted. It would mean that where familial pernicious anemia occurred alone, only the single hemic factor was disturbed on an hereditary basis; where familial posterolateral sclerosis occurred alone, only the neural factor would be involved; and where both pernicious anemia and posterolateral sclerosis were found to occur in a family, multiple hereditary factors would have to be postulated. On the other hand, if the hemic and neural factors are shown to be identical, the hereditary features of subacute combined degeneration of the spinal cord might have to be explained by some predisposition or susceptibility of the neural parenchyma itself. At this stage of our ignorance only fruitless, indecisive speculation can exist. All further genetic formulations would seem to depend on future observations on the etiology of these 2 conditions. However, we feel that wherever hereditary factors are found in pernicious anemia and/or in subacute combined degeneration of the spinal cord, such clinical studies should be added to the literature so that an eventual future genetic evaluation will be more sound and acceptable.

**Summary and Conclusion.** 1. Clinical and laboratory findings of identical twins with subacute combined degeneration of the spinal cord, gastric achlorhydria, and recovery with liver therapy are reported.

2. The monozygosity of the brothers was established on the basis of identical physical characteristics, blood groups, and finger and palm prints.

3. These cases are thought to strengthen the concept of heredity as one of the etiologic factors in the development of posterolateral sclerosis.

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# PROGRESS OF MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF  
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### RENAL DECAPSULATION FOR OLIGURIA AND ANURIA

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SURGEONS who decapsulate kidneys in the expectation of increasing urinary flow usually justify themselves by assuming that the operation either diminishes intrarenal pressure or denervates renal blood-vessels. Other less plausible theories have been devised but these are the 2 most popular and of them the former is more widely held because of numerous clinical assertions that anuric kidneys often look swollen to the naked eye and that capsulotomy results in bulging of the renal parenchyma through the incision. Attractive as these theories may be in their simplicity, the actual basis upon which they rest seems slim indeed. Furthermore, it is so difficult to see how decapsulation can achieve anything approaching total denervation of the kidney that this review will confine itself to a consideration of the evidence that increased intrarenal pressure is an important factor in the production of the oliguric state.

It is conventional to deal with this problem by offering first a classification of the anurias. We are quite unable, however, to subdivide them in any satisfac-

tory manner and, indeed, are prepared to suggest that no attempt to do so be made since it seems that diverse etiologic factors all produce anuria chiefly by the same fundamental mechanism; that is, increased tubular reabsorption of glomerular filtrate. Whether this broad generalization is strictly accurate or not, the familiar breakdown of the anuric phenomenon into: (a) *prerenal*, *renal* and *postrenal*, or (b) *glomerular* and *tubular varieties*, appears extravagant to us because a large variety of renal insults has been shown to initiate a series of events which culminates in apparently identical tubular lesions. Important as *prerenal* influences may be,<sup>42,54,70</sup> it is obviously not possible, for example, to diminish the rate of renal blood flow markedly without also affecting the nutritional status of the tubules, nor can the rate of glomerular filtration be appreciatively reduced without simultaneously offering the tubules a greater opportunity to exert their reabsorptive powers. By the same token *postrenal* obstruction is as certain to increase the rate of tubular reabsorption as it is to

diminish the minute output of glomerular filtrate. Since the volume of urine in the bladder is known to depend much more upon tubular than upon glomerular function, a brief summary of the effects of renal anoxia, nephrotoxic agents and obstruction of the lower urinary tract upon tubular structure and function may serve to justify this somewhat unitarian viewpoint and to place decapsulation in a proper perspective.

EFFECTS OF RENAL ANOXIA UPON THE TUBULES. No effort has been made to provide a complete bibliography of this relatively new but important field, but it is believed key references are included. Maeraith, Havard and Parsons<sup>91</sup> were apparently the first to attempt a unified explanation for the anuria which occasionally complicates a large and diverse number of prerenal conditions by suggesting that renal anoxia rather than hypothetical nephrotoxins or mechanical blockage of the tubules is the responsible agent. In an excellent review, Lucké<sup>79</sup> employs the term "lower nephron nephrosis" to describe the essentially similar degenerative lesions frequently found in conditions associated with destruction of tissue and intravascular hemolysis. He also emphasizes the importance of circulatory changes in the kidneys but believes that toxic chemicals and mechanical blockage of tubular lumens by protein precipitates may be contributing factors. His study, based upon 538 fatal cases accumulated by the Army Institute of Pathology, shows that essentially similar clinical and pathologic pictures of renal insufficiency have been produced by a large number of conditions—battle wounds and crushing injuries, abdominal operations, burns, transfusion reactions, sulfonamides, chemical poisons, heat stroke, blackwater fever, hemolytic anemias, obstetrical complications, acute pancreatitis and rickettsial diseases. The kidneys are described as usually swollen and somewhat enlarged; microscopically, the glomeruli seem relatively bloodless but otherwise normal, whereas the thick limbs of

Henle's loops and the distal convoluted tubules show degenerative changes of variable degree and the lumens are here and there filled with pigmented casts. Interstitial edema, cellular infiltration and venous thromboses are also seen in the medullary portions of the kidneys. Interest in these lesions was originally aroused by the British descriptions of traumatic uremia and the "crush syndrome."<sup>18,20,21,37,93</sup>

By means of renal clearance technics it was soon shown that the application of a tourniquet to a dog's leg causes prompt reduction in renal blood flow and urinary output and that tubular function remains depressed for a considerable length of time after release of the tourniquet and disappearance of shock;<sup>24c</sup> but these authors noted no residual anatomic lesions in the kidney. Others, however, have described degenerative cellular changes in the kidney tubules following adequate mechanical constriction of the renal artery.<sup>85,123,124</sup> Phillips and co-workers<sup>111</sup> have shown that renal blood flow must be tremendously diminished before tubular function is impaired; but Corcoran and Page<sup>24b</sup> demonstrated that intense renal vasoconstriction does take place after skeletal injury. Lauson, Bradley and Cournand<sup>75</sup> have shown that in shock renal blood flow and glomerular filtration rate are reduced to a much greater extent than can be accounted for by the reduction in systemic arterial blood pressure, apparently as a compensatory effort on the part of the kidneys to counterbalance anoxia in other more vital organs. These authors agree with Corcoran and Page,<sup>24b</sup> and with Selkurt<sup>124</sup> that impairment of renal function may persist long after the circulatory disturbances elsewhere have been corrected.

Similar renal abnormalities have been described in conjunction with other kinds of circulatory disturbances—non-crushing injury,<sup>30,104,107</sup> hemorrhage,<sup>24,24b,71,111,125</sup> heat stroke,<sup>92</sup> burns,<sup>14,56,100,127</sup> obstetrical trauma,<sup>11,101,106,149</sup> sulfonamide intoxication,<sup>51,52,80,97,110</sup> incompatible blood transfusion,<sup>2,9,28,32,33,44,79,91,114</sup> retroplacental hemorrhage,<sup>148</sup> alkalosis,<sup>53,87,99</sup> diabetic coma,<sup>62</sup>

anemia,<sup>10</sup> pernicious anemia,<sup>48</sup> vomiting,<sup>15</sup> hematemesis,<sup>7,157</sup> Addison's disease,<sup>133</sup> enzyme shock<sup>93</sup> and congestive heart failure.<sup>116,126,138</sup>

These renal lesions have also been described in infectious diseases in which, although specific tubulo-toxins may be suspected, circulatory collapse is also common—cholera,<sup>23</sup> yellow fever,<sup>41</sup> and Weil's disease.<sup>61</sup> In blackwater fever similar episodes of renal failure frequently occur<sup>50,51,88,89,90,137,142</sup> as they may rarely in other hemolytic crises,<sup>22,53,60,67,86,95</sup> but here the possible toxic effects of hemoglobin derivatives can scarcely yet be separated from the circulatory changes. The part the pigments play will be discussed in the section on Nephrotoxins.

The "hepatorenal syndrome," a loosely defined combination of hepatic disease and renal failure, has been attributed on unproved grounds to the nephrotoxic action of hepatic substances.<sup>143</sup> It seems more likely, however, that no such syndrome exists and that the occasional case of renal failure associated with jaundice is due to circulatory changes resulting from shock, dehydration, anemia, chemical changes in the body fluid and infection, all of which factors may produce renal anoxia and artificial degeneration. There seems to be no reason to search for specific toxins.

Renal anoxia can hardly be supposed to play an uncomplicated rôle in glomerulonephritis, malignant hypertension and bilateral cortical necrosis of the kidneys where obstructive lesions in the glomeruli markedly reduce filtration rate and allow more complete reabsorption of tubular fluid.<sup>24a,35,36</sup>

Finally, extremely interesting observations have recently been made which, if confirmed, may explain the anurias of reflex or emotional origin. Trueta and his colleagues<sup>5,135,136</sup> have claimed that appropriate stimulation of peripheral nerves can divert the entire renal blood supply from its usual glomerular route directly to peritubular channels supplying only the medulla, the consequence being that

glomerular filtration and urinary formation may partly or wholly cease without concomitant reduction in total renal blood flow. They regard this as a possible homeostatic mechanism which prevents loss of fluid (urine) from the kidney in conditions of shock and protects the glomerular apparatus from noxious agents. They feel that renal cortical ischemia can be produced centrally or peripherally through a variety of mechanisms, and that the different types of anuria just described may be of neurogenic origin. The implication is made that these anurias should be treated by spinal anesthesia or splanchnic block rather than by transfusion or decapsulation. These important claims should certainly be thoroughly explored, particularly since the reported experiments have been done only in rabbits which have an extremely labile glomerular system anyway. Barclay, Cooke and Kenney<sup>4</sup> have expressed skepticism about these claims, saying that changes in the cortical circulation are of relatively minor importance in the determination of urine volume in man. Wolf<sup>145,146</sup> has shown that pain itself can greatly diminish renal blood flow and suggests that diseased kidneys may not recover from such an insult. Cubitt<sup>25</sup> states that shock in the usually accepted sense is not a necessary precursor of the reflex anurias which may follow traumatic procedures. Although the mechanism of the anurias produced or accompanied by changes in the general circulation is not well understood, there is little evidence from these studies that increased intrarenal pressure is an important factor.

EFFECTS OF THE NEPHROTOXIC AGENTS UPON THE TUBULES. The rôle which toxic products of tissue or blood destruction play in the production of renal insufficiency is far from clear. There is some evidence that circulating toxins appear in traumatic shock.<sup>39,40,113</sup> It was originally suggested that in "crush syndrome" degeneration of the distal convoluted tubules might result from precipitation of hematin in acid and concentrated tubular fluid,

and there seems to be no doubt that certain heme derivatives are cytotoxic.<sup>24,24b</sup> Flink<sup>44</sup> found that the amount of renal damage was proportional to the plasma hemoglobin concentration. Recent surveys, however, indicate that the excretion of hemoglobin derivatives is not the sole cause of tubular damage<sup>60,79,91,147</sup> and it is emphasized that these hemolytic disorders are often accompanied by circulatory disturbances which may involve the kidney to an important degree even though the superficial evidences of shock are not apparent.<sup>30,88,107,134</sup> Hemolytic crises have not been uncommon after the administration of certain sulfonamide derivatives;<sup>49</sup> but anuria may also be produced by mechanical blockage of the lower urinary tract with precipitated crystals. The effects of sulfonamide therapy on the urinary tract have been ably reviewed by Peterson and Finland.<sup>110</sup>

Hormonal influences have also been invoked as a cause of certain forms of oliguria. Brun and co-workers<sup>16</sup> have shown that the suppression of urine which follows prolonged standing is associated with the release of antidiuretic hormone into the blood stream. Bradley<sup>10</sup> suggests that the neurohypophysis becomes activated in hypoproteinemic states because of the loss of water into the tissues and consequent concentration of the plasma. Postoperative anuria may be due in part to hyperpitressinemia occasioned by peripheral sensory stimulation according to the mechanism of neurohypophyseal control described by Rydin and Verney.<sup>121</sup> Pitressin cannot properly be called a nephrotoxin, of course, but it does act upon the renal tubules to promote water absorption. The antidiuretic material detected in some edematous and oliguric states has not been absolutely identified as pitressin, however, and it should be remembered that the hormone cannot reduce urinary flow very much if the urine is already concentrated.<sup>130</sup> The importance of this type of oliguria, therefore, remains to be established.

Some heavy metals are known to be

extremely toxic to renal tissue. Richards' direct observations on the frog's kidney<sup>119</sup> showed clearly that glomerular filtration (and presumably renal blood flow) was unaffected at the time that *mercure* had so damaged the tubules that the glomerular filtrate was being blindly and totally reabsorbed into the peritubular blood stream before it could leave the kidney. By means of clearance techniques it has also been shown that *uranium* can destroy tubular function without appreciatively affecting renal blood flow.<sup>8</sup> Page, Taylor and Kohlstaedt<sup>102</sup> have described the profound renal functional changes in *arsenic* poisoning. Forbes<sup>46</sup> found tubular degeneration in a case of *carbon tetrachloride* poisoning, as did Lucké,<sup>79</sup> who also includes cases of *mushroom* and *alcohol* poisoning in his "lower nephron nephrosis syndrome." In all these conditions oliguria is best explained by the reabsorption of glomerular filtrate through damaged tubular epithelium, and there seems to be no need of invoking swelling of the kidney to explain it.

EFFECTS OF OBSTRUCTION OF THE LOWER URINARY TRACT UPON THE TUBULES. It is conceivable that urinary formation may be impeded either by edema of the kidneys or by precipitation of material within the tubular lumens but there is little in the literature to suggest that either event occurs to such a degree as to raise intrarenal pressure above glomerular filtration pressure. Pathologists have evidently not been struck by any appreciable increase in the water content of anuric kidneys. This may be a postmortem artifact, but the observations of surgeons may also be deceptive since Culpepper and Martin<sup>27</sup> have noted that even gentle handling of the living dog's kidney results in an increase of intrarenal pressure measured directly. The matter of intrarenal pressure is discussed later; it is sufficient to say here that nothing is really known about the pressure exerted by interstitial edema in renal disease. Obstruction of the ureter or renal vein would certainly raise intrarenal pressure to an important

level but would not, of course, be logically treated by decapsulation.

It is also generally now thought that tubular obstruction by casts or precipitated pigment is a relatively unimportant factor in reducing urinary flow.<sup>2,51,79,91</sup> It has been repeatedly observed, for example, that spontaneous diuresis in these conditions is not accompanied by any outpouring of casts or cellular detritus. Except, therefore, for the rare instances of neoplastic or lymphomatous infiltration of the kidney, increased intrarenal pressure due to intratubular hydronephrosis appears to be an unimportant cause of anuria.

**INTRARENAL PRESSURE.** Despite all the assertions that increased intrarenal pressure is an important etiologic factor in anuria, we have failed to discover any recorded instances in which this pressure has been measured. Neither have we found any reliable direct estimations of normal intrarenal pressure. Brodie<sup>13</sup> attempted to measure the general tension of the renal substance within the capsule during active diuresis but his technique was not described and his admittedly inaccurate results indicated a tension of about 40 mm. Hg, a figure which is almost certainly too high. Winton<sup>144</sup> made certain observations on isolated blood perfused kidneys of the dog which allowed him to calculate a hypothetical intrarenal pressure under those abnormal conditions. He found that a rise in ureteral pressure would fail to affect the urinary flow unless it exceeded a certain level, often about 10 mm. Hg. He attributed this to intrarenal pressure exerted laterally on some distal part of the tubules which kept them collapsed until they were forced open by urine under pressure just in excess of that in the renal tissue. Based upon that idea, indirect determinations of intrarenal pressure were made by measuring the ureteral pressure which must be exceeded to produce a perceptible fall in urinary flow. His figures varied from 4 to 14 mm. Hg, with a typical value of 10 mm. Hg. Winton states that

decapsulation commonly halves this intrarenal pressure and that diuretics will elevate the pressure to 20 or 30 mm. Hg. From theoretical considerations of an "artificial nephron," Peters<sup>108</sup> states that an increase of a few millimeters of mercury in intrarenal pressure is sufficient to cause oliguria or anuria, predicts that bilateral decapsulation will reduce intrarenal pressure by about 50% and advises immediate operation whenever it is suspected that tubular dilatation, interstitial edema, inflammatory exudate, swelling of tubular epithelial cells, or invasive neoplasms may be causing intracapsular enlargement of the kidneys. Similar recommendations were made for the treatment of post-transfusion anuria,<sup>109</sup> but no statistics or case reports are offered.

Accurate measurement of the interstitial fluid pressure in the mammalian kidney is almost a technical impossibility because of its anatomic position and because bleeding results from the smallest puncture. One of us (W. S. C.) attempted to measure intrarenal pressure under various conditions by a method similar to that used by Henderson and associates,<sup>62</sup> Burch and Sodeman,<sup>17</sup> and Wells and co-workers<sup>141</sup> in their various studies on intramuscular, subcutaneous and intracutaneous pressures. The apparatus consists of a No. 22 needle with lateral openings, a calibrated adapter with 1 mm. bore containing isotonic sodium citrate, and a water manometer with rubber bulb attachment for varying the pressure upon the citrate column in the glass adapter. When the pressure in this system is raised, the intrarenal pressure is taken to be that at which the fluid column just begins to move into the tissue.

Preliminary acute experiments have shown this intrarenal pressure to be profoundly influenced by ureteral pressure, systemic blood pressure, venous pressure, the state of the renal arterioles, and induced diuresis. As previously stated, mere handling of the kidney in an anesthetized dog has produced the appearance of renal congestion, darkening

in color, and a rise in intrarenal pressure to a level about twice that of normal. In a small series of unanesthetized dogs with kidneys explanted to the lumbar region, Culpepper<sup>26</sup> also made repeated intrarenal pressure determinations through small nicks in the skin. Results varied in the normal animal from about 7 to 21 cm. of water with an average of about 16 cm. of water.

If it is assumed that increased intrarenal pressure may cause anuria, what is the mechanism of production? Does intrarenal pressure obstruct the outflow of blood or urine or of both? Stropeni<sup>131</sup> and Hülse and Litzner<sup>68</sup> have observed that decapsulation increases renal blood flow in dogs, but apparently no one has studied the matter in trained conscious animals by modern clearance techniques.

As for the possibility of intrarenal pressure obstructing the outflow of urine in the kidney, it can only be said that we do not know. However, Winton<sup>144</sup> is of the opinion that even in the normal kidney the intrarenal pressure is not an insignificant hindrance to urinary flow down the tubules; were the pressure removed entirely he believes the urinary flow would be 50 to 100% higher. Hence, it is not inconceivable that elevated intrarenal pressure from various causes may obstruct the outflow of both the blood and urine from the kidney, but until experimental studies of intrarenal pressure in anuric animals before and after decapsulation have been made, we shall not know whether decapsulation is indicated in the treatment of human anuria.

**DECAPSULATION.** The clinical reports of experiences with decapsulation are even less persuasive than the physiologic and pathologic observations. This is the situation possibly because no one reporter has had extensive experience but also because the protocols are usually incomplete, the diagnoses often uncertain, and the expected mortality rates under conservative management but crudely understood. It is certain too that failures are apt not to

be recorded so that the statistics are heavily weighted in favor of surgical cures. We have examined the English literature over the past 20 years with the following results.

*Postoperative and Reflex Anuria.* Successful decapsulation for anuria following appendectomy in children has been reported 3 times.<sup>47,65,66</sup> Hyman<sup>69</sup> had the same experience in another child in whom anuria developed after multiple fractures and surgical correction. Muschat and co-workers,<sup>98</sup> and Hall<sup>59</sup> each reported a recovery from anuria following ureteral dilatation and cystoscopy, but Lowsley and Harbach<sup>78</sup> had 2 deaths under comparable circumstances.

*Crush Syndrome.* We found only 1 case report<sup>84</sup> and that patient died. Bywaters<sup>19</sup> states that when the syndrome is ordinarily recognized, one may expect only about one-third of the patients treated to recover.

*Postpartum Anuria, Including Cortical Necrosis.* Three successful experiences<sup>23a, 74,112</sup> must be contrasted with 4 fatalities.<sup>31,72,101</sup>

*Post-transfusion Anuria.* Eight recoveries have been reported by as many authors.<sup>34,45,81,103,115,117,132,150</sup> Prior to this, Beraud<sup>6</sup> reported a failure and Bancroft<sup>3</sup> a recovery. The mortality rate in this small group of cases certainly compares favorably with the overall mortality rate of 52% in the 200 cases collected by Hesse<sup>64</sup> and the similar mortality rates in reports of smaller series by Bordley,<sup>9</sup> Daniels and associates,<sup>28</sup> and Goldring and Graef.<sup>55</sup> It may be that these experiences lend support to the recommendations of Peters,<sup>108</sup> particularly if the operation is done early. The military experience in the last war has not yet been reported, but numerous personal communications suggest that it was not encouraging.

*Sulfonamide Nephrosis.* Although difficult to do so, we have tried to exclude those cases in which the anuria was apparently due wholly or in large part



to obstruction of the lower urinary tract by crystals. The cases are too few in number to be of great significance, but 6 successful cases of decapsulation for anuria associated with sulfonamide nephrosis<sup>73,76,97,129,139,140</sup> and 1 death<sup>43</sup> have been reported.

*Chemical Nephrosis.* Eight cases of mercuric chloride poisoning have been reported with 5 recoveries<sup>12,63,105,118,122</sup> and 3 deaths.<sup>1,94,122</sup> Recoveries following poisoning due to bismuth<sup>151</sup> and saponated cresol<sup>77</sup> were seen, but death followed operation in 1 case in which the anuria was attributed uncertainly to methyl alcohol.<sup>128</sup> The bichloride series is certainly not large enough to justify comparison with medically treated cases.

*Nephritis.* Although the rationale for treating glomerulonephritis is not clear to us, we have included 2 cases of patients who survived both the operation and the disease<sup>36,58</sup> and 3 who did not.<sup>85a,120</sup>

Thus, a total of 48 cases of anuria have been treated by decapsulation with a total mortality rate of about 32% (15 cases). Exactly half of these were subjected to unilateral operation only, and the mortality rate for this group of 24 cases was 16.6% (4 cases). Among the 24 cases in which both kidneys were decapsulated the mortality rate was 45.8% (11 cases).

It would, of course, be foolish to deny the possibility that interstitial edema contributes to the oliguric state, particularly in the face of descriptions like that of Reid, Penfold and Jones,<sup>117</sup> who decapsulated a pair of kidneys for post-transfusion anuria: "Both kidneys presented the same appearance: about twice the normal size, dark blue, and as firm as a tennis ball but less elastic. The capsules seemed very tense, a pale blue friable kidney bulged through the lines of incision owing to increased intracapsular pressure. The left kidney almost exploded and pieces of friable tissue were taken for microscopy." Directly opposed to this is a statement by O'Sullivan and Spitzer<sup>101</sup>

who decapsulated kidneys in 2 cases of acute renal failure following abortion: "We could not convince ourselves that the kidneys in these cases were under tension at operation and we considered the operation tilted the scale rapidly against the patients." Consecutive case reports of post-transfusion anuria in the same issue of 1 journal arrive at contradictory conclusions; 1<sup>103</sup> attributes recovery to unilateral decapsulation, although 6 days after operation the blood urea nitrogen rose from 400 to 600 mg. per 100 cc., whereas the other<sup>29</sup> saw spontaneous diuresis on the 12th day with a blood urea nitrogen of 320 mg. per 100 cc. These citations illustrate the confusing clinical descriptions and emphasize the need for further experimental work.

**Conclusion.** Important as a large variety of prerenal influences may be in precipitating urinary suppression, the existing evidence favors the belief that the most important factor in maintaining the oliguric state is the appearance of tubular lesions which permit excessive reabsorption of glomerular filtrate. Little experimental, pathologic and clinical evidence has been found to support the belief that increased intrarenal pressure is a significant feature although it may be true that decapsulation has usually been performed too late.

A review of the literature on the subject in English for the past 20 years indicates that, with the possible exception of post-transfusion anuria decapsulation has not improved the recovery rate from anuria due to circulatory disturbances in the kidney or to toxic nephrosis. On the contrary, it suggests that if decapsulation is going to be done at all, it should be restricted to 1 kidney. Much experimental work is needed on the subject of intrarenal pressure. Until this is forthcoming, decapsulation of the kidney for the relief of anuria or oliguria must be regarded as an empirical therapeutic measure of unproved value.

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Addendum. Attention is called to a symposium published since this review was prepared. (Bell, E. T. and Knutson, R. C.: *J. Am. Med. Ass'n.*, 134, 441, 1947; Corcoran, A. C. and Page, I. H.: *J. Am. Med. Ass'n.*, 134, 436, 1947; Martineau, P. C. and Hartman, F. W.: *J. Am. Med. Ass'n.*, 134, 429, 1947; and Moon, V. H.: *J. Am. Med. Ass'n.*, 134, 425, 1947).

## NEUROLOGY AND PSYCHIATRY

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## ELECTROENCEPHALOGRAPHY

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WHEN Newman<sup>74</sup> in 1938, in this same publication, reviewed the status of electroencephalography, the electroencephalograph had been in use in the United States for approximately 3 years. Since the first of January 1938 until July of 1946, 842 articles which are concerned with some aspect of electroencephalography are listed in the Cumulative Index Medicus. It is evident that a large amount of work has been done in this field and considerable progress has been made.

Today the electroencephalograph is firmly established as an accepted and reliable laboratory procedure. This has been accomplished in spite of the fact that its possible value, and especially the incidence of cortical dysrhythmia in certain conditions, has continued in unabated dispute. However, to such competent investigators as Dr. and Mrs. Gibbs, Jasper, Lennox, Robert Schwab, Kornmüller, Gray Walter, the Davis' and others, we owe the basic and sound principles of electroencephalography without which continued advancement would be impossible.

Unfortunately this examination is not available to many physicians in the United States. This was very evident in a recent unpublished survey made by one of us

(F. G. E.) concerning graduate neuropsychiatric training in North America. It was surprising to find that many medical schools and institutions of good reputation have no functioning electroencephalograph laboratory. Many of these schools and hospitals stated that a laboratory would be set up if and when a trained electroencephalographer would join its staff; furthermore, there are many cities of approximately  $\frac{1}{2}$  million population or less which do not have this service and there are several states which have no electroencephalograph functioning within their boundaries.

CLINICAL APPLICATIONS. To the practising physician the contribution of the electroencephalogram as a diagnostic aid in those patients complaining of seizures is one, if not the most important, of its uses in clinical medicine. Lennox<sup>59</sup> has estimated that at least 1 person in 200 (0.5% of the general population) in the United States have or have been subject to recurrent seizures. It is obvious that such a large group of severely handicapped individuals present an economic as well as hygienic problem to our nation. To accurately diagnose, treat and, perhaps, someday prevent the occurrence of epilepsy is directly concerned with electro-

encephalographic findings. It is generally accepted that between 80 and 90% of unselected adult epileptics will show evidence of cortical disturbance by electroencephalographic examination.<sup>18,24,30,85</sup> It is true that a rather large percentage of epileptics have a type of electroencephalographic abnormality which at present can only be regarded as a non-specific type of disturbance. Perhaps in the years to come these "non-specific" disturbances will be understood and used as a therapeutic guide. Until the work of Lennox,<sup>58</sup> the attempts to use the electroencephalogram as a therapeutic guide were very discouraging.

Lennox found a definite correlation between type of seizure, electroencephalographic abnormality and the therapeutic response to tridione. He describes these types of clinical seizures, which he calls pyknoepilepsy, myoclinic epilepsy and akinetic epilepsy. If patients with such seizures had electroencephalograms showing a 3 per second spike wave (Fig. 1 C) the therapeutic result following the administration of tridione was excellent. This electroencephalographic abnormality is a specific one, and has been referred to by Gibbs and Lennox as the "petit mal" type of dysrhythmia. Lennox also found that patients with similar clinical seizures, but with other types of electroencephalographic changes (Fig. 1 D) did not respond favorably to the administration of tridione.

Although epilepsy has always been thought to have an hereditary predisposition, it is amazing to find that the available information regarding this important subject is relatively meager. Again, Lennox and Gibbs<sup>60</sup> are the leading contributors. Their studies on monozygotic and dizygotic twins leaves little room for doubt as to the influence of heredity on the configuration of the brain wave pattern. A person may have an abnormal brain wave pattern without manifesting clinical seizures.<sup>56</sup> This individual, if the abnormality can be considered of cryptogenic origin, actually carries a predisposi-

tion to epilepsy. Lennox has arrived at several definite conclusions based on electroencephalographic findings which are concerned with the advisability of epileptics marrying and having children. He<sup>57</sup> states "The marriage of 2 normal persons who both carry a predisposition to seizures is worse than the union of an epileptic with a person who has no predisposition—a 'normal' person who carries a predisposition is as likely to have an epileptic offspring as an out and out epileptic." Lennox also believes that "the hereditary factor in epilepsy is about the same as in diabetes, one-half that in obesity and one-eighth that in migraine."

Many investigators<sup>14,33,45,107</sup> have studied the relationship of electroencephalography to post-traumatic epilepsy. Its value as a guide for surgical removal of the irritated area is of special importance.<sup>79</sup>

Penfield and Erickson,<sup>80</sup> working with Jasper, state that the presence of a 3 per second spike and wave (the petit mal pattern) practically rules out possible surgical intervention. However, the presence of focal electroencephalographic abnormality makes further investigation mandatory. As a rule, the post-traumatic epileptic is more apt to have a dysrhythmic electroencephalogram than is the patient with cryptogenic seizures. The post-traumatic epileptic is much more likely to have a focal disturbance (Fig. 1 B) but at times latent focal changes may pass undetected. Walker<sup>102</sup> has apparently partially solved this problem by studying the records of patients suspected of post-traumatic epilepsy during the injection of small amounts of metrazol. A previous latent abnormal focus is apt to appear, revealing the area of localized brain pathology.

Accurate information of the incidence of electroencephalographic changes in post-traumatic conditions has increased considerably.<sup>8,15,33,35,37,41,53,54,76,79,80,95,100,105</sup> This gain was largely at the expense of numerous service men injured in the line of dut

However, this new knowledge was put to good use and frequently, on the basis of an electroencephalogram, the disposition of a soldier was decided. The electroencephalogram was of particular importance in those individuals who had suffered a head injury and continued to have subjective complaints, but had no positive ab-

normal neurologic findings. The progressive improvement, the degree of abnormality, its presence or absence, were all used by the military physician in the evaluation of the post-traumatic condition. From Noell's<sup>76</sup> report it is obvious that the German military used this examination for similar purposes.

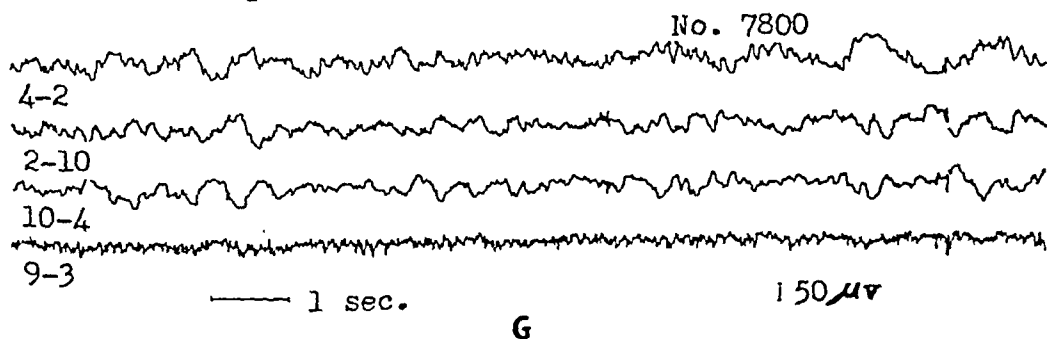
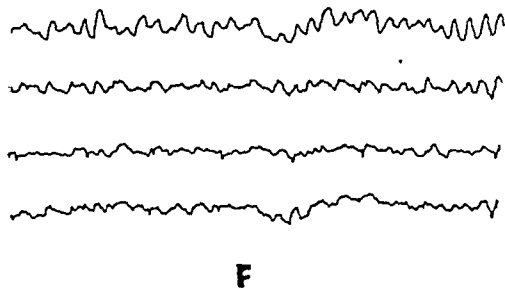
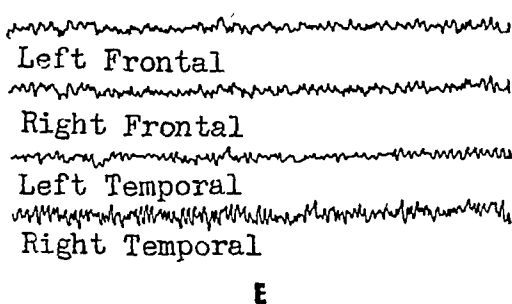
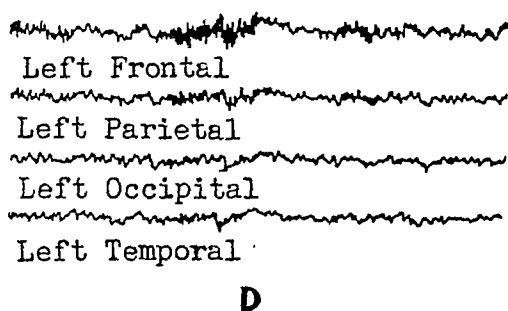
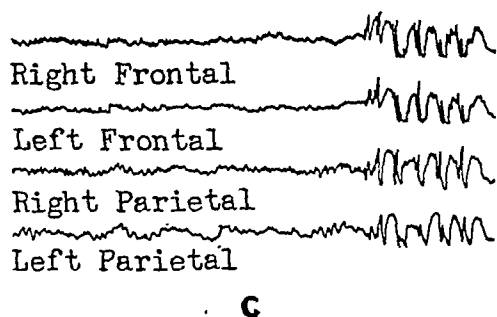
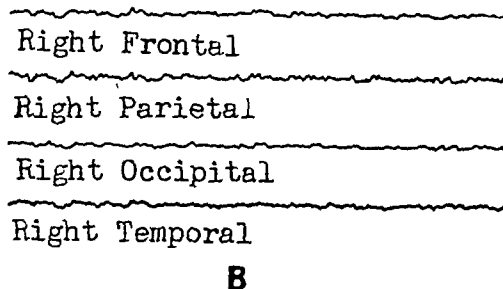
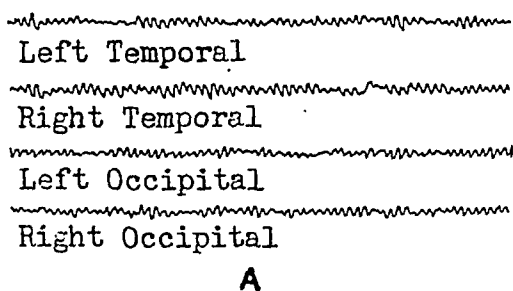


FIG. 1.—Normal EEG'S. A, 8.5 to 12 per second waves—alpha rhythm; B, low voltage fast activity—beta rhythm. Abnormal EEG'S. C, Three per second spike and wave—petit mal type; D, paroxysmal fast activity—grand mal type; E, symptomatic epilepsy (focal abnormality in fourth channel, compare to third); F, slow waves following a severe head injury; G, phase reversal in a brain tumor.

\* Terms used by Gibbs and Lennox.

It is evident that minor head injuries produced very transient changes in the electrical cortical activity.<sup>15,105</sup> In the severe head injuries, in those patients free of seizures, there frequently is a gradual improvement in the record up to 2 years after the injury. If the patient suffers from post-traumatic epilepsy, the improvement of the electroencephalogram is negligible over a comparable period of time.<sup>33</sup> Patients who have suffered head wounds with dural penetration are much more apt to have electrical cortical changes than those with closed head injuries. Williams<sup>106</sup> found that the pattern was disturbed in 94 % of the patients examined. Kornmüller<sup>53</sup> found 37 % slightly disturbed and 50 % very disturbed. One of us (E. W. B.) found a slightly lower percentage of disturbed electroencephalograms in a series of 103 patients with penetrating wounds of the skull<sup>8</sup> (Fig. 1 F).

In civilian life the introduction of the electroencephalogram as evidence in medico-legal disputes is gaining in use. This rather complex subject has been recently reviewed by Gibbs.<sup>32</sup>

Electroencephalographic localization of expanding intracranial lesions (Fig. 1 G) has shown little, if any, improvement since the report by Williams and Gibbs in 1938.<sup>108</sup> A very extensive study of intracranial neoplasms was recently presented by Hoefer, Schlesinger and Pennes.<sup>44</sup> Their review included 543 cases of brain tumors of which approximately 70 % were localized by electroencephalograms. Deep seated tumors and posterior fossa tumors are responsible for most of the non-localizable tumors. Smith, Walter and Laidlow<sup>97</sup> report good localization of posterior fossa neoplasm but this is certainly not the rule.

The psychoses associated with chronic alcoholism,<sup>38,48</sup> syphilis,<sup>37</sup> arteriosclerotic and senile brain<sup>62</sup> disease, are all frequently accompanied by disturbed cortical rhythms. Both the severity of clinical symptoms and the presence of symptomatic epilepsy directly affect the degree and incidence of electroencephalographic abnormality.

Liberson and Seguin<sup>62</sup> have observed in arteriosclerotic and senile mental patients a much higher percentage of abnormal electroencephalograms if the patient exhibits the clinical symptoms of confusion and marked irritability. Greenblatt and Levin<sup>37</sup> found double (90 %) the incidence of abnormality in those patients with central nervous system syphilis and seizures as compared to those without seizures (44 %). In general, in all organic brain disease the abnormality of the electroencephalogram tends to parallel the clinical findings. However, it is possible to find normal rhythm in patients with severe mental changes. The mere presence of a normal electroencephalogram does not make the psychosis "functional" rather than organic.

The vague complaint of "fainting spells" or "black-out spells" is a difficult clinical and therapeutic problem. The etiologic factors of short periods of unconsciousness are numerous and include a hypersensitive carotid sinus mechanism, epilepsy and hysterical reactions. Levin, Katz and Greenblatt<sup>61</sup> studied a large series of patients with fainting spells and found that some patients had true epileptoid manifestations such as an aura, tongue biting, muscular rigidity or clonic movements during the attack. These patients showed a high percentage of electroencephalographic abnormalities and should be correctly diagnosed as having minor epileptic seizures. In addition there are some patients who display no epileptic-like signs yet have typical epileptic electroencephalograms. These patients respond to the usual anti-convulsant medications. Most patients with "fainting spells" will have normal inter-syncopal electroencephalograms. Engel and Romano<sup>52</sup> report that in those patients with true vaso-depressor or carotid sinus syncope, a diffuse slowing of the brain waves accompanies the period of unconsciousness. They<sup>52</sup> believe that if the patient has a "fainting spell" during the electroencephalographic examination and no change in cortical rhythm is recorded, the spell can be classified as hysterical.

However, other investigators<sup>26</sup> have reported little or no change in cortical rhythm during carotid sinus syncope particularly of the "cerebral type."

Wilson's<sup>109</sup> concept that narcolepsy and epilepsy are etiologically similar has resulted in confusion in the minds of clinicians because the electroencephalograms of narcoleptics are frequently negative. Cohn and Cruvant<sup>9</sup> claimed to have found in narcoleptics "wave forms similar to those most commonly observed with the epileptics." Judging from the evidence they present, we do not feel that their conclusions are wholly justified. Dynes and Finley<sup>16</sup> in a study of 22 cases found no electroencephalographic abnormalities which would indicate a relationship to epilepsy. Blake, Gerard and Kleitman<sup>4</sup> expressed the opinion that normal sleep could be distinguished from narcoleptic sleep by the precipitous onset of sleep waves in the latter condition. It appears that, from an electroencephalographic standpoint, the only confirmatory evidence in the support of the diagnosis of narcolepsy rests upon the occurrence of a spell of uncontrollable sleep during the recording with an accompanying precipitous onset of sleep waves.

The medical literature concerned with the incidence and importance of disturbed electroencephalograms in behavior problem children, adult psychopathic personalities and criminals is confusing and filled with contradictions. Following the initial report of Jasper, Solomon and Bradley,<sup>46</sup> many authors have published electroencephalographic studies of children with behavior disorders and have found, according to their criteria, a high percentage of cortical dysrhythmias.<sup>6,7,34,46,67,96</sup> These percentages range upward to almost 90%. Some of the reports state that the abnormality most frequently found resembles or is identical with that encountered in epilepsy. However, Secunda and Finley<sup>86</sup> have expressed the opinion that the abnormality is an immature rhythm which is not commensurate with the patient's chronologic age. It has also been stated

that enuresis, which reflects immaturity, is the only neurotic trait that occurs in positive association with abnormal electroencephalograms.<sup>71,72</sup> Based on the assumption that the disturbed cortical rhythm is in some way connected with the antisocial or undesirable behavior, drug therapy has been attempted and good results reported. Cutts and Jasper<sup>10</sup> reported beneficial results with benzedrine. Lindsley and Henry<sup>68</sup> agreed that benzedrine produced "strikingly improved behavior" and also found dilantin of value. The favorable behavior response following dilantin medication has been confirmed by others,<sup>103</sup> but all agree that phenobarbital should not be used and that no appreciable alteration can be observed in the electroencephalograms. Some people have reported an increase in the incidence of electroencephalographic abnormalities in behavior disorders or poorly adjusted children, yet are very cautious in their conclusions.<sup>26,71,72,93</sup> Solomon, Brown and Deutscher<sup>93</sup> commented: "Studies and results to date do not warrant further interpretation or clinical application in diagnosis, therapy or prognosis."

Jenkins and Pacella<sup>47</sup> agree that abnormal electroencephalograms are frequent in certain delinquency problems and they attribute this to an "organic" factor. They conclude that: "Electroencephalography does not contribute to the explanation of most cases of delinquency. Most instances of stealing, particularly group stealing and kindred activities, do not suggest the presence of an organic factor; rather, the contrary. These cases do not show a high incidence of abnormal EEG'S."

Numerous investigators<sup>42,43,50,87,88,90</sup> reported a high percentage of electroencephalographic abnormalities in persons diagnosed as a "psychopathic personality" and in criminals. Silverman<sup>87,88</sup> reports that 75 to 80% of criminal psychopaths have abnormal or borderline tracings. Gibbs, Bloomberg and Bagchi<sup>28</sup> in a preliminary report tended to support Silverman's findings. In the subsequent



publication<sup>24</sup> they corrected their evaluation of EEG normality with the factor of age and found no significant correlation between the EEG and the type of criminal behavior. They concluded: "Since the EEG is a fairly reliable indicator of epilepsy and organic brain disease, it seems reasonable to conclude that subclinical forms of these disorders are not contributing factors in a significant fraction of the 'sane' criminal population." In a study of persons diagnosed as constitutional psychopathic state in a military setting, Simon, O'Leary and Ryan<sup>89</sup> found a somewhat higher incidence of abnormal records than would be expected in a group of normal controls but were unable to find any relationship "between the severity of different manifestations of psychopathy and the incidence of abnormality in records."

The types of normal rhythms which occur in the psychoneurotic individual and the patient suffering from a functional psychosis is an intriguing but extremely complex subject which is difficult to evaluate. The complexity is aggravated by the numerous systems which have been employed in analyzing the records as to the preponderance, presence or deficiency of certain frequencies of brain waves. It is possible that more accurate and consistent results will be obtained with the use of an analyzer similar to that developed by Walter.<sup>104</sup>

Most of the electroencephalographers agree that beta waves, or low voltage fast activity, are more frequently found in excess in psychoneurotic individuals<sup>5,94</sup> than in a normal control group. However, a good or dominant alpha rhythm has been reported in patients with duodenal ulcers<sup>43,93</sup> and asthma<sup>84</sup> believed to be on a psychosomatic basis. Large amounts of beta activity (low voltage fast) and weak alpha rhythms are reported in schizophrenias, while a high incidence of manic-depressive patients are said to have a "strong" or "medium strength" alpha rhythm.<sup>11,55</sup>

**PHYSIOLOGIC AND PATHOLOGIC INVESTIGATIONS.** In the last 9 years the most

important advance in the interpretation and evaluation of electroencephalograms, in our opinion, centers upon the realization that the age of an adult is a factor which must always be considered when one speaks of a normal electroencephalogram. Berger,<sup>3</sup> Lindsley,<sup>65,66</sup> and Smith<sup>91,92</sup> reported the characteristics of the electroencephalograms of children and the normal progression from slow to faster activity which occurs from infancy to adulthood. Davis<sup>12</sup> observed the changes in cortical rhythm which accompany old age and Greenblatt<sup>39</sup> and Gibbs<sup>29</sup> reported that fast activity increases until the approximate age of 55, after which a decline in frequency is the expected trend. It was previously reported that the degree of slowing produced by hyperventilation is related to the patient's age.<sup>31,63</sup> This slowing is referred to by Gibbs as a "build-up" and the response of marked slowing or a "big build-up" decreases in frequency as the age of the subject advances.

The fluctuations of cortical rhythm which are produced by variations in blood sugar levels are now well known.<sup>13,21</sup> The misleading findings of increased slow waves which can result if a record is made after prolonged fasting are now avoided. Sensitivity to hyperventilation which accompanies hypoglycemia is expected and taken into consideration.<sup>23,64</sup> Attacks of spontaneous hypoglycemia<sup>81</sup> are accompanied by a slowing of the brain waves which definitely explains the mental symptoms and may have some diagnostic value. Strauss and Wechsler<sup>98</sup> have observed that psychoneurotics have "an unusual lability of the EEG to hyperventilation in the presence of normal blood sugar values." They also found a relationship between nervous complaints in the morning and the development of delta activity during hyperventilation in the fasting state.

Güttner and Bonkáló<sup>40</sup> reported that fatigue was accompanied by changes in cortical rhythm. Kornmüller<sup>62</sup> in his recent book described the appearance in the frontal lobes of choppy activity, poor

alpha rhythm and occasional slow waves in both acute and chronic fatigue states. Barnes and Brieger<sup>2</sup> examined 26 medical students and 1 professor "before the beginning of a typical day of classes and at the end of it." They failed to find any electroencephalographic change which could be considered evidence of mental fatigue. Kornmüller, at least in part, based his observations on the examination of aviators with flying fatigue which is not analogous to the condition of the medical students. Under any circumstances continued investigation is certainly justified.

Dynes<sup>17</sup> recently brought to attention the interesting previously observed phenomenon<sup>69</sup> that there is no distinct difference in the electroencephalogram of a person in a hypnotic trance and in the normal waking state. He points out that the hypnotic state is often spoken of as "an artificial sleep" or "sleep-like state." Just what hypnosis is, is still unexplained, but from the electroencephalographic findings it can be concluded that it is not a sleep variant.

Although there is no direct correlation between electroencephalographic abnormality and migraine,<sup>95</sup> an interesting electroencephalographic observation was made by Engel, Ferris and Romano. They had previously encountered, in a study of decompression sickness, a migraine-like syndrome.<sup>20</sup> Focal electroencephalographic abnormality was recorded during the scotoma of the migraine-like headache. Because of the similarity between this syndrome and true migraine, electroencephalograms were obtained on 3 subjects with migraine while experiencing scotomas. In all 3, abnormal electrical activity from 1 occipital cortex was demonstrated. This finding is evidence in favor of localized vasospasm which results in the scintillating scotoma.<sup>19</sup>

Electric shock, metrazol shock and insulin coma therapy all produced changes in the electrical rhythm of the cortex. Insulin treatment<sup>49</sup> results in a comparatively mild slowing of the rhythm, while

metrazol<sup>51</sup> and electric shock<sup>78</sup> therapy produce more drastic changes. The degree of slowing, as would be expected, is influenced by the number of treatments and the time interval between each shock. Some patients seem to have a cortical rhythm which is resistant to change but this is a variable factor. The post-treatment abnormal electroencephalogram gradually returns to normal in a few weeks to a year after the termination of treatment. Some patient's electroencephalograms never return to normal, but a pre-shock EEG of such patients usually show evidence of a cortical dysrhythmia. Spontaneous convulsions have been reported following convulsive shock therapy. The 2 cases reported by Pacella and Barrera<sup>77</sup> had brain wave tracings prior to shock which were abnormal. It is probable that the treatment precipitated latent convulsive tendencies. Attempts have been made to correlate the pre- and post-shock electroencephalographic findings with clinical improvement, but the results have been of little value. One group<sup>99</sup> working entirely with schizophrenics found that the presence of an abnormal pre-shock tracing indicated a poor prognosis. A second group<sup>1</sup> which studied both schizophrenics and psychoneurotics were cautious in their conclusions, but felt that: "There is a suggestion that patients with pre-shock borderline-abnormal EEG's profit more as a group by shock treatment than those with normal EEG's."

TECHNICAL CONSIDERATIONS AND THE FUTURE OF ELECTROENCEPHALOGRAPHY. During the past decade the manufacturers of electroencephalographs have improved their machines and undoubtedly will continue to do so with the return of critical material to civilian use. Repeated attempts have been made to devise a simpler method for applying the electrode to the scalp. Several mechanical methods which involve a headgear<sup>70,101</sup> have been developed as well as a clip-on electrode<sup>75</sup> and an adhesive non-drying electrode paste.<sup>100</sup> Only experience will prove whether or not

these techniques have any real advantage over the time-honored use of collodion applied electrodes.

Although the knowledge of electroencephalography has increased considerably, it has been somewhat hindered by lack of standardized techniques and uniform interpretation of electroencephalograms. Controversy has arisen over certain methods of frequency analysis and their validity. This is really a wholesome normal progression of events and is to be expected if advancement is to continue. During the year 1946 the formation of the Eastern Association of Electroencephalographers was a definite step forward and provided the much needed opportunity for group discussion. The recent organization of the American Society of Electroencephalographers may provide this and other advantages to the electroencephalographers throughout America.

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# BOOK REVIEWS AND NOTICES

**DIAGNOSIS IN STERILITY.** Proceedings of Conference Sponsored by The National Committee on Maternal Health, Jan. 26-27, 1945, New York City. Edited by EARL T. ENGLE. Pp. 237. Springfield, Ill.: Charles C Thomas, 1946. Price, \$5.00.

THIS volume assembles in a very readable form a considerable amount of the current thinking upon the problems encountered in the investigation of infertile couples. Its contributors are experts in their respective fields. The chapters on semen analysis are very informative. Each chapter in the book includes a discussion by various members of the conference, and the papers are all ably and interestingly summarized by Dr. Rock. The volume of necessity does not cover completely all aspects of the subject. It would have been of considerable interest if a paper had been included upon the timing of ovulation as recently reported elsewhere by Farris. In spite of the limited field of topics presented at the conference, the volume is well worth the attention of everyone concerned in the treatment of human infertility.

D. M.

**EXPERIMENTAL HYPERTENSION.** By WILLIAM GOLDRING, RICHARD J. BING, EDUARDO CRUZ COKE, W. D. COLLINGS, L. W. DONALDSON, M. L. GOLDBERG, HARRY GOLDBLATT, B. GOMBERG, ARTHUR GROLLMAN, C. A. JOHNSON, OLIVER KAMM, LUIS F. LÉLOIR, H. MINATOYA, W. G. MOSS, ERIC OGDEN, IRVINE H. PAGE, JOHN W. REMINGTON, L. A. SAPIRSTEIN and G. E. WAKERLIN. Being the Results of a Conference on This Subject Held by the Section of Biology, of The New York Academy of Sciences, Feb. 9 and 10, 1945, New York City. Pp. 179; 60 ills. New York: New York Academy of Sciences, 1946. Price, \$3.75.

THIS timely monograph deals primarily with recent advances in the study of humoral and chemical factors in clinical hypertension, and the renal type of experimental hypertension. It is tersely written, with appropriate introductions, summaries, illustrations and bibliographies. For one wishing to bring himself up-to-date in this field it will make most profitable reading. W. J.

**A TEXT BOOK OF CLINICAL NEUROLOGY.** By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine (Neurology), Univ. of Southern California; Senior Attending Physician (Neurology), Los Angeles County General Hospital. 2nd ed. Pp. 699; 190 ills. New York: Paul B. Hoeber, 1946. Price, \$7.50.

THE 2nd edition of this excellent textbook embodies the advances occurring in the 5 years elapsing since the 1st edition. The sections on electroencephalography, the physiology of the basal ganglia and cerebral cortex, and the use of the sulfonamides have been revised, and new sections on toxoplasmosis, the use of penicillin in neurologic diseases, and the syndrome of neuromuscular exhaustion have been added. The author's style is lucid, and the presentations of the subject matter clear and concise. He incorporates his extensive personal experience, rather than presenting merely a warmed-over compilation of the literature. The book is highly recommended both for students and general practitioners, while specialists in the field will find it interesting reading.

C. R.

**SOME CHAPTERS IN CAMBRIDGE MEDICAL HISTORY.** By SIR WALTER LANGDON-BROWN, Emeritus Professor of Physic in the University of Cambridge. Pp. 119. Cambridge: at the University Press; New York: Macmillan, 1946. Price, \$1.75.

BASED on a series of lectures to the Royal Society of Medicine, this account of Cambridge medical history extends over 4 centuries. It emphasizes Carlyle's dictum that "history is the shadow cast by a few great men." Thus, there are considered such men as Caius, Gilbert, Glisson, Heberden, Haviland, Paget, Humphrey, Foster and Allbutt. They are used in turn to illustrate the Revival of Learning, the Dawn of Experiment, the Insurgent Century, the Age of Reason, the Beginning of Reform, the Rise of the Medical School, and the Transition from the Nineteenth Century. To those who have seen the summaries of these lectures in the *Proceedings* of the Royal Society of Medicine, and who heard with regret of the passing of their cultured and

philanthropic author, this more concrete form of the material is welcome; for medical Cantabrigians it should furnish a useful record; to almost any intelligent person it should provide pleasant and profitable reading.

This is a book for a larger public than its title seems to invite, not only because of the good selection of subject matter, which touches on far more than Cambridge medicine, but because of the author's entertaining style.

E. K.

**HUMAN GENETICS.** By REGINALD RUGGLES GATES, B.Sc., Ph.D., M.A., LL.D., Fellow of the Royal Society; Emeritus Professor of Botany, Univ. of London; Hon. Chairman, Bureau of Human Heredity; Past Vice-President of the Eugenics Society, the Royal Anthropological Institute, the Linnean Society; Past President of the Royal Microscopical Society; sometime Associate Professor of Zoology, Univ. of California. 2 vols. Pp. 1518; 326 ills. New York: Macmillan, 1946. Price, \$15.00.

THIS book is intended as a survey of modern developments in the field of human heredity. Though written from the point of view of a biologist, much of it deals with subjects of great medical importance. The scepticism of many physicians in regard to the findings of the geneticists may be due partly to the experimental basis of the science, largely a study of heredity in plants and lower animals. It is only in recent years that human genetics, proceeding necessarily by analogy rather than experiment, has acquired a large body of knowledge.

For broad scope and clear presentation of an immense amount of detail this book by Gates is unique in its field. Here one can easily find material dealing with practically every hereditary variation and abnormality that has been described. Though much of the discussion is interspersed with lengthy citations of work done on lower forms, these asides are quite relevant in that they demonstrate the types of material from which theories of human heredity are derived.

The first volume deals chiefly with the heredity of variations and abnormalities of organs and organ systems. General principles of heredity in man are rather briefly treated, an elementary knowledge of genetics being assumed. A chapter is devoted to eye

and hair color, another to color blindness, a third to disorders of the skeletal system. Other systems are considered in a similar manner. The heredity of the blood groups, very actively investigated in recent years, is given an excellent and up-to-date presentation.

In the second volume such topics as allergy, cancer, susceptibility to disease, hereditary syndromes and anthropologic characters are taken up. The reader will find many controversial points on which the author gives rather summary opinions. These range from cases where there is actual question of whether a disorder is inherited or not, *e. g.*, Hodgkin's disease, to the finer points of genetics such as the use of the concept of "penetrance." Anyone desiring further information will be greatly aided by the hundreds of well-annotated references at the end of each chapter.

The paper is a fairly good war time product, the printing and the charts very clear. Genetic symbolism adopted by the Federation of Eugenic Organizations is used throughout. The relatively few photographs are for the most part reproductions, and, though of only fair quality, illustrate the various conditions sufficiently well.

The author is to be congratulated for assembling this most complete reference work on an important and neglected subject, and particularly for providing the interested physician with a key to its vast literature.

C. B.

**NEW ASPECTS OF JOHN AND WILLIAM HUNTER.** By JANE M. OPPENHEIMER, Bryn Mawr College. Foreword by FENWICK BECKMAN. Pp. 188; 5 ills. New York: Henry Schuman. Price, \$6.00.

To the large body of Hunteriana a skilful writer here adds 2 essays—"Everard Home and the Destruction of the John Hunter Manuscripts" and "William Hunter and His Contemporaries." Working as a Guggenheim Fellow at Yale and then at Bryn Mawr College, she has culled from the mass of the data sufficient evidence to show that though Home behaved unwisely "his actions were not those of a guilty man." Nor does she believe him guilty—rather that he foolishly omitted formal acknowledgment of his debt to "the powerful little man of five foot two who dominated medical science in

his century." "In Great Britain" should have been added.

Of William Hunter's less important career, Miss Oppenheimer selects a comparatively unknown side—his meddling in politics and his contacts with Queen Charlotte, Pitt, Walpole and others of the aristocracy. Neither aspect, however, appears to be either edifying or entertaining, though both confirm the estimate of his narrow fallibility—his "skew path to imagined power" and "a willingness to compromise his integrity" that was the antithesis of the nature of his greater younger brother. E. K.

**PRINCIPLES IN ROENTGEN STUDY OF THE CHEST.** By WILLIAM SNOW, M.D., Director of Radiology, Bronx Hospital, Roentgenologist in Charge, Harlem Hospital, New York. Pp. 414; 508 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, \$10.00.

This is another book on the chest which explores a phase slightly different from conventional texts. It is not an atlas and it is not a text. The descriptions of lesions are given in a short and abbreviated style very much as one would prepare an abstract. Many of the physiologic and pathologic considerations have been completely omitted. The author has not attempted to consider many of the excellent contributions to the study of chest diagnosis. He does consider bronchial spasm, carbon dioxide tension, and

lung circulation briefly but almost excludes considerations of the dynamics of the lung, about which so much has been written and which is so important in the consideration of any interpretation of lung lesions.

As one reads the text the lack of reference material is felt. The illustrations, some of which are good and some poor, have inadequate legends and the majority have no history. One feels the need for illustrations made in views other than many of those included in the publication. The lack of emphasis on differential diagnosis is apparent throughout.

The arrangement of the illustrations in this book is most unusual. Some are arranged symmetrically and are pleasing to the eye and others are off-set, protruding into the margin, and the legends are not well placed. The index does not refer to any of the illustrations but merely refers to the subject matter; on turning to the subject matter one may find no reference to any illustrations of relatively well-known and common lesions.

The publisher as usual has provided excellent paper for his book and the print is pleasing to the eye. The illustrations of good negatives are excellent, but there are a number of illustrations which do not show the lesion that the author intended to demonstrate and this is in spite of the fact that both space and size of illustrations are adequate. E. P.

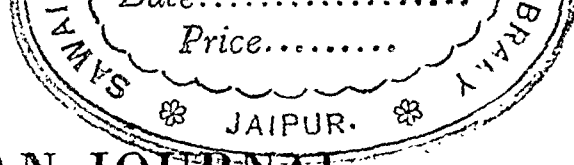
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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### GYNECOMASTIA DUE TO INFECTIOUS HEPATITIS OF THE HOMOLOGOUS SERUM TYPE

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CLINICAL observations and experimental studies suggest that gynecomastia is due usually to a disturbance in hormonal activity. Although hyperestrinism may be the most important factor,<sup>6,16</sup> gynecomastia has also occurred after the administration of androgen<sup>19</sup> and desoxycorticosterone,<sup>15,22</sup> and in conditions associated with an increase in gonadotropic hormone,<sup>5,7,14</sup> and a decrease in the 17-ketosteroid<sup>24</sup> excretion. In the present state of our knowledge it is not known whether these observations indicate that gynecomastia can be produced by a variety of unrelated disturbances, or whether they all act through a common mechanism, possibly in the pituitary.

Clinical evidence of an endocrine disturbance is obvious in some cases of gynecomastia, as, for example, in those associated with tumors of the adrenals,<sup>18,26</sup> pituitary<sup>29</sup> and testes,<sup>5,7</sup> and in those occurring with puberty,<sup>11</sup> atrophy of the testes,<sup>2,14</sup> and hyperthyroidism.<sup>28</sup> In many cases, however, the endocrine system appears to be normal. As the physiology of the hormones is elucidated and as better methods of assaying hormone activity become available, it should be possible to determine the pathogenesis of all types

of gynecomastia. This development is well illustrated in the case of the gynecomastia associated with cirrhosis, which has been recognized for a long time,<sup>3</sup> but which has only recently been found to be due to a disturbance in estrogen metabolism.<sup>9</sup>

It is reasonable to suppose that a similar disturbance may occur in other types of liver disease and may lead to gynecomastia. Indeed, an increased excretion of estrogen has recently been found in infectious hepatitis.<sup>8</sup> We now wish to report the occurrence of gynecomastia in 2 patients with this disease.

**Case Reports** CASE 1. L. E. C., a 32 year old soldier, incurred a compound comminuted fracture of the left tibia when struck by an enemy shell fragment on Jan. 11, 1945. He was removed to a hospital where he received appropriate surgical treatment, including several infusions of plasma. On April 8 he was transferred to the Schick General Hospital for further surgical treatment.

The *past history* revealed a penile lesion with positive Wassermann reaction in 1937. Inadequate antisyphilitic treatment was administered for an indefinite period thereafter. In 1943 asymptomatic neurosyphilis,



with positive blood and spinal fluid, was discovered. A course of artificial fever therapy was given, the results of which are not known.

*Physical examination* on April 8, 1945, revealed nothing of note except an incompletely healed compound fracture of the left tibia and the residuals of frost-bite of the toes. The liver was not palpable and the genitalia were normal. No note was made of the condition of the breasts, but the patient, at a later date, maintained that they were normal at this time. There were no abnormal neurologic findings.

*Laboratory studies* revealed a normal blood count and urine. The blood Kahn test was positive. The spinal fluid exhibited Group I changes of neurosyphilis.

The patient's course in the hospital was uneventful during the 1st month. On May 14, approximately 4 months after the last infusion of plasma, he developed nausea, diarrhea and dark urine. Four days later clinical jaundice appeared and the liver was palpated 3 cm. below the costal margin. There was no hepatic tenderness and the spleen was not palpable. Studies at this time revealed a 1 minute serum bilirubin of 4.5 and a total serum bilirubin of 7.2 mg. %, a positive test for bile in the urine and normal prothrombin level. A few days later the serum proteins were found to be low with a normal albumin-globulin ratio. The thymol turbidity reaction and the sedimentation rate were normal. A diagnosis of acute homologous serum hepatitis was made. The patient was kept at complete bed rest and a diet high in carbohydrate and protein and low in fat was administered.

During the following 4 weeks the jaundice increased in intensity and there was marked lassitude, anorexia and weight loss. At no time was there nausea or vomiting. Shortly after the onset of jaundice the liver receded behind the costal margin and could never again be palpated. At no time was there splenomegaly, ascites or edema. Because of the anorexia and poor dietary intake, daily infusions of 1 to 2 liters of 10% glucose were given from June 4 to June 15. In addition, 25 gm. of concentrated human serum albumin were given intravenously on June 6, 7 and 8 and 500 cc. of plasma on June 9. The serum protein level, which was slightly depressed before treatment, showed a transient rise, especially in the albumin fraction.

The prothrombin level fell slightly during the first 2 weeks of jaundice, but in the 3rd week it fell precipitously to 20% of normal. Although there was no bleeding from the skin or mucous membranes, vitamin K therapy was instituted. The patient received 8 mg. daily, intramuscularly, from June 8 to July 21. The prothrombin level rose very slowly, reaching 67% of normal in 3 weeks. In part, at least, the rise could be attributed to the improvement in liver function that occurred at that time.

The jaundice reached its peak at the end of the 4th week, by which time the total serum bilirubin had attained a level of 36.2 mg. %. From then on there was rapid improvement in the patient's general condition. All his symptoms subsided, his appetite returned, and he regained the weight he had lost. The jaundice, however, faded very slowly. Clinical icterus did not clear up until the 15th week of the disease and the serum bilirubin did not return to normal until the 22nd week. Although the patient felt well and there were no overt signs of liver disease, there was evidence of liver damage as late as 37 weeks after the onset of jaundice, as evidenced by the retention of 22% of injected bromsulphalein (5 mg. per kg.) at the end of 45 minutes. The liver and spleen were not palpable. There were no signs of portal obstruction. There were no spider nevi and no palmar erythema.

On July 1, approximately 7 weeks after the onset of jaundice and 3 weeks after it had begun to fade, the patient first noted symmetrical enlargement and tenderness of the breasts. They gradually increased in size over a period of 5 weeks. Examination at that time revealed slight fatty enlargement of both breasts. The nipples and areolas appeared normal and there was no secretion. A small, firm, tender nodule was palpable beneath each areola. The attending surgeon who saw the patient at this time believed the masses were fibroadenomata and recommended excision. The patient, however, refused to submit to operation. During the following 8 weeks the enlargement and tenderness of the breasts gradually subsided, so that they no longer appeared abnormal. Nevertheless, a freely movable, moderately firm, non-tender and smooth mass, measuring 2 cm. in diameter, could still be felt beneath the areola of the

right breast as late as Feb. 11, 1946, 7 months after the onset of gynecomastia. At no time were there other stigmata of an endocrine disturbance. The patient was well developed physically. He exhibited no unusual distribution of fat. The beard and the hair on the trunk were of the normal male type. The external genitalia were well developed. The blood pressure remained normal.

The results of the liver function studies, briefly outlined above, are enumerated in Table 1.

note except for the left leg which was encased in a plaster cast. There was no obvious malnutrition, although the patient was not weighed. The genitalia were normal and there were no stigmata of any endocrine disturbance. No note was made of the condition of the breasts, although in retrospect the patient maintained that they were normal at this time.

Laboratory studies on admission revealed a normal blood count and urine. The blood Kahn test was negative. Culture of the wound yielded a heavy growth of penicillin-

TABLE 1.—LIVER FUNCTION STUDIES IN CASE 1

Date	1-min. serum bilirubin (mg. %)	Total serum bilirubin (mg. %)	Bromsulphalein retention (%)	Serum protein (gm. %)	Serum albumin (gm. %)	Serum globulin (gm. %)	Prothrombin level (% of normal)	Cephalin-cholesterol flocculation	Thymol turbidity (units)	Hippuric acid excretion (gm.)	Urine urobilinogen (units)	Urine bile test
5/18/45	4.50	7.20	..	4.80	3.80	1.00	100	..	3	..	..	..
5/21/45	..	..	..	4.80	3.80	1.00	75	..	3	..	..	..
5/25/45	..	..	..	6.06	3.54	2.52	77	..	3	..	..	..
6/ 8/45	21.20	36.10	..	6.02	3.61	2.41	20	÷/1+	2	..	5.75	..
6/11/45	22.20	36.20	..	6.15	4.35	1.80	37	..	3	0.32	..	..
4/14/45	13.10	23.00	..	4.75	3.27	1.48	42	2+/3+	2	..	..	4+
6/26/45	..	..	..	4.83	2.87	1.96	67	..	..	..	..	..
ONSET OF GYNecomastia												
7/ 1/45	..	..	..	..	..	..	..	..	..	..	..	..
7/11/45	3.70	7.12	..	..	..	..	..	..	4	..	..	..
7/28/45	1.42	2.90	..	..	..	..	..	..	3	..	..	..
8/ 6/45	1.12	1.87	..	..	..	..	..	..	3	..	..	..
8/15/45	0.75	2.25	..	..	..	..	..	..	3	..	..	..
8/25/45	0.55	1.25	..	..	..	..	..	..	3	..	..	..
8/31/45	0.45	1.07	..	..	..	..	..	..	1	..	..	..
9/ 8/45	0.35	1.70	..	..	..	..	..	..	2	..	..	..
10/15/45	0.15	0.60	23	..	..	..	..	..	2	..	0.34	..
10/20/45	..	..	..	..	..	..	..	..	..	..	0.66	..
10/22/45	..	..	..	..	..	..	..	..	..	..	0.63	..
12/10/45	0.07	0.45	15	..	..	..	..	..	3	..	..	..
1/29/46	0.07	0.70	22	..	..	..	..	..	3	..	..	..

Methods employed described in previous communications.<sup>12,23</sup>

Normal values: 1 minute serum bilirubin = 0.2 mg. or less; total serum bilirubin = 1 mg. or less; bromsulphalein retention at the end of 45 minutes (5 mg. kg.) = 5% or less; serum protein = 6 gm. or over; serum albumin = 4 gm.; cephalin-cholesterol flocculation = less than 1+ in 24 hours and 2+ in 48 hours; thymol turbidity reaction = less than 5 units; hippuric acid excretion (1.77 gm. sodium benzoate intravenously) = 0.7 to 0.9 gm.; urine urobilinogen (2 hour excretion) = less than 1.3 Ehrlich units.

CASE 2. E. J. P., a 28 year old soldier, incurred a compound comminuted fracture of the left calcaneus, astragalus and cuboid when struck by enemy shell fragments on Oct. 16, 1944. He was removed to a hospital where he was given multiple transfusions of whole blood and plasma. The following day the wounds were débrided. Since the posterior tibial artery was completely severed it was tied off. A week later secondary closure of the wound was attempted. The wound failed to heal completely, so that the patient was returned to the United States.

He was admitted to the Schick General Hospital on Jan. 19, 1945, at which time physical examination revealed nothing of

resistant *Streptococcus fecalis* and *Bacillus pyocyaneus*.

Course: On January 22, the cast was bivalved. Roentgenograms were taken and a new cast was applied. Immediately following this procedure the patient developed nausea and anorexia. A few days later the urine became dark in color, and on February 6 clinical jaundice became evident. The liver was enlarged 3 cm. below the costal margin and was tender. The spleen could not be felt and there was no fever. The total serum bilirubin was 7 mg. % with an immediate direct van den Bergh reaction. The cephalin-cholesterol flocculation reaction was 3+. The serum total proteins

were 5.5 gm. % with a relatively normal albumin-globulin ratio. A diagnosis of acute homologous serum hepatitis was made. The onset of symptoms had occurred 14 weeks after the last transfusion of blood and plasma.

A high carbohydrate, high protein, low fat diet was ordered for the patient, but he ate very little for the first 3 weeks, losing 20 pounds in weight. The jaundice increased in depth during the first 2 weeks and the liver increased in size, descending 8 cm. below the costal margin. On February 21, the total serum bilirubin reached its maxi-

marked leukopenia. The leukocyte count was 1950 per c.mm., with 11% polymorphonuclears, 45% lymphocytes, 11% atypical lymphocytes, 14% monocytes; 15% eosinophils, and 4% plasma cells. The red blood cell count remained normal. There was a slight reduction in the platelet count to 170,000 per c.mm. There was no lymphadenopathy, splenomegaly or ulceration of the mucous membranes. The heterophil agglutination test for infectious mononucleosis was negative. Although a drug reaction was suspected it was not proved. The epididymitis healed completely within 1 week

TABLE 2.—LIVER FUNCTION STUDIES IN CASE 2

Date	1-min. serum bilirubin (mg. %)	Total serum bilirubin (mg. %)	Serum protein (gm. %)	Serum albumin (gm. %)	Serum globulin (gm. %)	Serum cholesterol (mg. %)	Cholesterol esters (% to total)	Serum alkaline phosphatase (units)	Prothrombin time (control-pt.) (sec.)	Ceruloplasmin-cholesterol flocculation	Thymol turbidity (units)	Urine bile test	Urine urobilinogen (units)	Hippuric acid excretion (gm.)
2/ 6/45	17.00	16.60	5.50	3.10	2.40	170	15	9.9	14/14	3+/4+	8	4+	1.85	0.45
2/ 9/45	19.60	30.70	5.50	3.30	2.20	170	15	20.0	15/21	4+/4+	8	4+	1.00	
2/10/45	13.40	24.50	6.05	3.10	2.95	170	15	17.0	14/22	3+/4+	8	4+	1.31	
2/12/45	20.00	29.00	6.30	3.70	2.60	213	46	15.0	16/20	3+/3+	8	3+	2.64	
2/21/45	12.50	27.50	6.30	3.70	2.60	220	62	15.5		3+/3+	8	3+	37.00	
2/26/45	9.50	21.53	5.75	13.25				12.0		3+/3+	8	1+	28.80	
3/ 1/45	5.75	12.00	5.75	12.00				12.8		3+/3+	8	0	24.80	
3/ 3/45	3.00	6.50	5.75	12.00				12.8		1+/1+	6	0	2.80	
3/ 6/45	2.13	5.13											4.95	
3/ 8/45	0.50	1.75												
3/10/45	0.65	1.00												
3/26/45														
3/27/45														
4/14/45														
4/19/45														
4/24/46														2.18
4/26/45														4.24
4/27/45														5.46
9/21/45														

Normal values as in Table 1; serum cholesterol = 150 to 250 mg.; cholesterol esters = 40 to 70% of total cholesterol; serum alkaline phosphatase = below 5 Bodansky units.

um level of 35.5 mg. %. There was a concomitant progressive deterioration of parenchymal function, as indicated in Table 2. During the period of poor dietary intake parenteral glucose, human serum albumin and vitamins were administered. At the height of the jaundice the prothrombin level of the blood fell. Large doses of vitamin K were given, but very little effect was noted.

On February 17, during the 4th week of hepatitis, the patient developed an acute, non-suppurative epididymitis on the right. Three days later he developed chills and fever, pain in the teeth and gums, and

and was thought to be related to an attack of gonorrhea in the past. The patient was given several transfusions and large doses of penicillin, totaling 2,160,000 units, between February 18 and 24. The fever subsided in a few days and the blood count returned to normal a few days later.

Marked clinical improvement occurred following the subsidence of fever in the 6th week of the disease. Appetite returned and the patient began to gain weight. Hepatic tenderness subsided and the liver edge began to recede toward the costal margin. Jaundice, however, faded much more slowly and did not disappear until the 12th week,

although the serum bilirubin level was still slightly elevated then. As indicated in Table 2, the return of liver function paralleled the subsidence of jaundice, although the excretion of urobilinogen was still abnormally high in the 14th week.

During April 1945, in the 14th week of the disease when jaundice had subsided but when a mild degree of impaired liver function was still present, the patient noted a painful enlargement of the right breast. Examination revealed a conical fatty enlargement of the breast with a circumscribed mass of moderately tender glandular tissue, about 4 cm. in diameter, beneath the areola. The mass was freely movable beneath the areola and over the underlying tissues, but appeared to be attached to the nipple. The areola and nipple were normal and there was no secretion. A month later an identical mass appeared in the left breast. The attending surgeon suggested the diagnosis of adenofibroma of the breasts and recommended excision. The patient, however, refused to submit to operation. The tumors showed no change for 2 months and then began to get smaller. The mass on the right disappeared in July 1945, about 3 months after its appearance. The one on the left was still present in September 1945, 4 months after its appearance. The liver was no longer palpable at this time and the serum bilirubin level and the thymol turbidity reaction were normal. Unfortunately no note was made of the condition of the genitalia.

**CLINICAL FEATURES OF GYNECOMASTIA COMPLICATING INFECTIOUS HEPATITIS.** The structural changes in the breasts observed in these cases were typical of gynecomastia. Unfortunately biopsy specimens were not obtained, so that the characteristic hyperplasia of the ducts and periductile tissues<sup>13,17</sup> was not demonstrated. The bilateral involvement of the breasts and their regression later make the initial diagnosis of fibro-adenoma highly improbable. Chronic mastitis can be excluded for the same reason and also because the usual inciting factor, trauma, was absent.

There were many striking similarities between these 2 cases. In both the gynecomastia was bilateral, although in Case 2 there was a 1 month interval between its

appearance on the 2 sides. There was a marked tendency toward regression. In Case 1 the gynecomastia had almost disappeared in 8 weeks, although small masses of glandular tissue could still be felt as long as 7 months after the onset. In Case 2 it cleared up completely on one side within 3 months, while on the other a small mass was still present at the end of 4 months. Breast enlargement occurred late in convalescence from hepatitis; in Case 1, 7 weeks after the onset of hepatitis and at a time when jaundice had largely subsided, and in Case 2, 14 weeks after the onset when clinical jaundice was no longer evident.

The hepatitis was of the homologous serum type in both instances, and, as is often the case in this form of the disease,<sup>23,27</sup> it was unusually severe, ran a protracted course, and was followed by residual impairment of liver function. In Case 1 the serum bilirubin attained a level of 36.2 mg. %, clinical jaundice lasted 15 weeks, and there was marked bromsulphalein retention at the end of 37 weeks. The peak of the serum bilirubin level in Case 2 was 35.5 mg. %, clinical jaundice lasted 12 weeks, and the urinary excretion of urobilinogen was still moderately increased in the 14th week. The occurrence of residual impairment of liver function following jaundice of this severity and duration is not surprising in the light of recent experience.<sup>12</sup> There were no physical findings, however, to suggest the development of cirrhosis, a complication of hepatitis encountered occasionally.<sup>4</sup> In neither case could the liver be felt during convalescence, and there was no evidence of collateral venous circulation, splenomegaly, ascites, spider nevi or palmar erythema.

**Comment.** The normal liver inactivated estrogen,<sup>30</sup> but in experimental liver injury<sup>1,10,25,29</sup> and in clinical cirrhosis<sup>9</sup> this function is seriously impaired. The gynecomastia that occurs in cirrhosis is thought to be due to the resultant hyperestrinemia,<sup>9</sup> but other factors may be contributory. Certainly atrophy of the

testes<sup>21</sup> and chronic malnutrition, which are common complications of cirrhosis, may play a rôle, since both may give rise to gynecomastia in non-cirrhotics.<sup>2,13,14,21</sup>

It is surprising that, with the recent increase in the incidence of infectious hepatitis, gynecomastia has not, heretofore, been reported as a complication. It is noteworthy, however, that both our cases suffered unusually severe and protracted jaundice. Evidently the factors responsible for growth of the breast must be operative over a long period or must come into play only after unusually severe liver damage to produce gynecomastia.

Cirrhosis and infectious hepatitis, especially when the latter is severe, share a common background of diffuse injury to the liver with a marked disturbance in many of its functions. It appears likely, therefore, that the pathogenesis of the gynecomastia that occurs in both conditions is the same. Unfortunately it was not possible to study hormone excretion in our cases. The recent work of Gilder and Hoagland,<sup>8</sup> however, suggests that hyperestrinemia is an important factor. They have found that there is an increase in estrogen excretion during the acute phase of infectious hepatitis in males, and that the increase is proportional to the severity of the disease. During convalescence the excretion rate falls, but does not reach normal for some time.

Just as in cirrhosis, atrophy of the testes and chronic malnutrition may con-

tribute to the development of gynecomastia in infectious hepatitis. Although the testes appeared normal, a decrease in 17-ketosteroid excretion has been noted in this disease,<sup>8</sup> suggesting that some degree of atrophy may have been present in our cases. Moderate weight loss occurred at the height of the jaundice, but the low initial serum protein levels (Tables 1 and 2) suggests that malnutrition was present even before the onset of hepatitis.

Since the breast lesion described subsides spontaneously, it is of importance to recognize its relationship to infectious hepatitis if needless surgery is to be avoided. The relationship is of particular interest to endocrinologists, since it affords a unique opportunity to study the pathogenesis of gynecomastia.

**Summary.** Bilateral gynecomastia occurred during convalescence in 2 cases of infectious hepatitis. The hepatitis was of the homologous serum type and ran a severe and protracted course, but there was no evidence to suggest the development of cirrhosis. The gynecomastia subsided spontaneously, so that early recognition of the relationship between breast lesions and hepatitis will preclude needless surgery. Hormone excretion studies in infectious hepatitis suggest that hyperestrinemia is an important factor in the pathogenesis of this type of gynecomastia. Testicular atrophy and malnutrition, however, may be contributory factors.

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## VARIOLATION AS A PRINCIPLE

IMMUNIZATION IN EXPERIMENTAL POLIOMYELITIS WITH ACTIVE VIRUS UNDER  
AUTARCEOLOGIC PROTECTION OF ESTROGENIC SUBSTANCE

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VARIOLATION is perhaps the oldest specific immunizing procedure. In spite of what, from the present-day point of view, was an enormous hazard it was widely used and during a whole century the subject of continuous investigation. With many attempts to make it safe by preparation of the patient, such as by the use of the cooling regimen of Sydenham so that the "solids and fluids may be reduced from a greater to less inflammability," as well as by modification of the virus to be inoculated by dilution or the use of unripe virus, it might well have led to an efficacious preventive procedure had it not been supplanted by vaccination, and declared a felony by act of Parliament in 1840.<sup>17</sup> If "it might have led to an efficacious preventive procedure" could be said of smallpox where subclinical immunization does not occur naturally, variolation as a principle (immunization through mild disease by inoculation of the "prepared" patient with active virus) should offer even greater possibilities in disease where subclinical immunization is the rule and disease the exception. But it has entered little, if at all, into later immunologic investigation. Certainly the central idea in artificial immunization has been modification or attenuation of virus. Little attention has been paid to "preparation of the patient."

If variolation was outlawed a little over a century ago, variolation as a principle (using the term in the same sense that Pasteur used Jenner's specific term "vaccination" to designate a general principle) may be coming back on the scene at this

precise time. Premarital exposure of females as a practicable preventive measure for the recently discovered congenital anomalies as a sequel to maternal rubella has been discussed in a recent paper.<sup>11</sup>

There are a number of examples of immunization where either advantage is taken of the prepared host, or where the procedure in a sense amounts to preparation of the host, though these procedures are perhaps probably more often looked upon as being in keeping with the legendary idea of "immunity from repeated bombardment with small subinfective doses." The first of these would be represented by measures aimed at the postponement of measles to an age when there is less likelihood of complications, that is, to an age when the patient is better "prepared" to withstand the attack. When looked at somewhat in reverse, the administration of convalescent serum or gamma globulin at the appropriate time after exposure to bring about a modified but immunizing attack of the disease, can likewise be regarded as an example of preparation of the patient. Another procedure which may actually amount to preparation of the patient, rather than modification of virus, is the employment of the interference phenomenon as in the use of complex vaccine in influenza. Ziegler and Horsfall<sup>22</sup> concluded that the first virus inoculation interferes with the multiplication of the second, not by multiplication *per se* nor by the action of one virus on the other, but probably resistance to the second virus is the result of a tissue alteration induced by the first virus.

Still another field, as yet quite unexplored, is that of biochemical interference.<sup>10</sup> It is not inconceivable that there may be inert substances with a chemical configuration and tissue tropism which would blockade a given but damaging virus-cell union (for example anterior horn cell in poliomyelitis) while immunization is being accomplished with active virus. Protective action of trypan red and certain related dyes against infection with certain neurotropic viruses has been shown although the mechanism involved was not elucidated.<sup>21</sup> In other words there is reason to believe there may be "heterologous" (chemical) as well as "homologous" (virus) interferants. Not inconsistent with the clinical observations of almost every investigator who has seen large numbers of cases, from Underwood in 1789 on, to the effect that poliomyelitis exhibits a preference for those "of strong and blooming constitution;" and in keeping with both the early observation of Rous<sup>19</sup> and the recent work of Schneider which more exactly assigns the rôle of dietary deficiency in susceptibility to infection,<sup>20</sup> new evidence that nutritional deficiency decreases susceptibility is at hand. The enhanced resistance of animals on dietary deficiency to a number of virus infections<sup>16,18</sup> is an example of "preparation of the host" where the development of immunity has not been investigated.

There are indications that in poliomyelitis factors in the host, rather than virus or exposure factors, may be a major determinant as between the development of the frank disease or of subclinical immunity upon exposure to the virus. Studies of the nature of these autarceologic factors<sup>2,4,5,6,7,8</sup> have led to experiments in which monkeys have been rendered more resistant to intranasal instillations of virus by administration of estrogenic substances.<sup>3,4</sup> That these experiments do not exactly reflect the mechanism of subclinical immunization in man, in spite

of the fact that intranasal instillation presumably is a method of inoculation of virus simulating natural infection, is indicated by failure of even repeated intranasal instillations of virus under the protection of estrogenic substances to immunize. As with intranasal chemical blockade<sup>9</sup> this failure to immunize suggests that in such experiments a complete blocking of entrance of the virus is accomplished. In the disease in man where the indications are that a single infection results in immunity, it would appear that the virus must reach some deeper structure to set up the immunizing process. That the locus of estrogen-induced resistance is not the central nervous system itself is shown by the fact that under its influence animals, although resistant to intranasal instillation, are fully susceptible to intracerebral inoculation.<sup>13</sup> In earlier experiments<sup>12</sup> it had been found that active virus injected subcutaneously or intracutaneously frequently resulted in immunization with relatively little hazard of disease. It would now appear therefore, that in experiments on enhancement of resistance to disease where immunization is the objective, a route of inoculation lying somewhere between intracerebral and intranasal instillation should be employed.

The present paper reports the effect of administration of alpha-estradiol benzoate\* on resistance of the mouse to *subcutaneous* injection of Mouse-Hamster strain<sup>14</sup> of poliomyelitis virus.† At the same time the possibilities of producing subclinical immunization rather than clinical disease by inoculation of the prepared host with active virus are investigated.

**Experimental.** *Effect of Alpha-estradiol Benzoate on Resistance.* One hundred normal albino mice weighing about 15 gm. and evenly divided as to sex were used in this experiment. Fifty were given a subcutaneous injection of 0.01 mg. of  $\alpha$ -estradiol benzoate 3 times weekly. The remaining

\* Progynon-B. Product of Schering Corporation.

† Anderson and Bolin<sup>1</sup> have reported enhancement of resistance to oral administration of the same virus by progesterone (complete protection), stilbestrol (mortality reduced from 68 to 2.5%), t-propionate (68 to 20%); desoxycorticosterone acetate failed to modify mortality.



mice received no treatment. Fourteen days after the initial injection of estrogen all mice were given a single subcutaneous injection of 0.02 ml. of a 10% emulsion of poliomyelitis virus prepared from brain of mice succumbing to the disease 4 to 5 days after inoculation. The results are shown in Chart 1. Sixty-two % of the prepared mice succumbed as compared with 84% of the untreated controls, a difference of exactly the same order as that obtained when intranasal instillation was employed.<sup>15</sup> Estrogen treatments were discontinued 11 days after virus injection and the surviving mice were later challenged for immunity.

Ten of the treated and 4 of the untreated mice withstood a third virus injection. The remaining mice were sacrificed and the blood sera collected for test for neutralizing substance.

*Virus Neutralization Tests.* The collected sera from mice that had received estrogen treatment and from untreated controls (all of which had withstood intraperitoneal challenge for immunity) were pooled separately. A third pool was made of normal mouse serum (serum controls). Each pool was thoroughly mixed with an equal amount of a 10% emulsion of poliomyelitis virus in a quantity sufficient to inject each of 6 mice

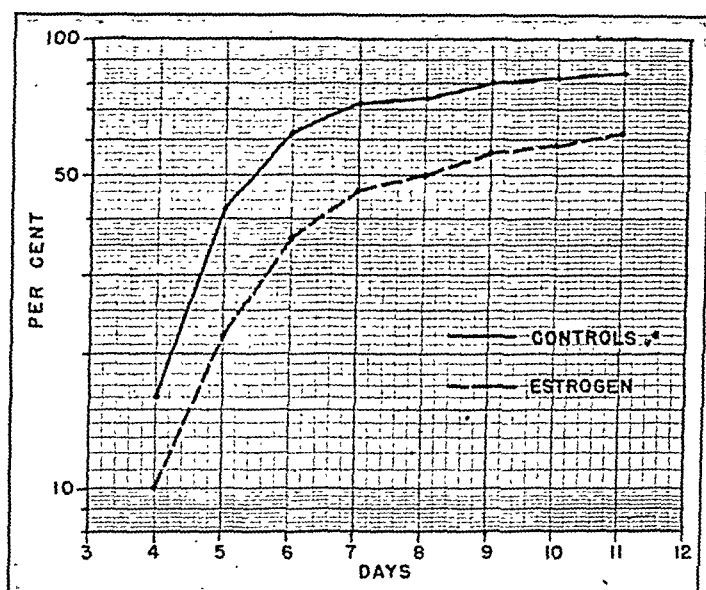


CHART 1.—Cumulative mortality. Estrogen treated and untreated control mice injected subcutaneously with M-H strain of poliomyelitis virus.

*Intraperitoneal Injection of Virus as a Test for Immunity.* Twenty-six days subsequent to subcutaneous injection of virus (15 days after the last mouse came down with the disease) all surviving mice, 19 treated and 8 untreated, were injected intraperitoneally with 0.05 ml. of a 10% emulsion of the same virus strain previously used. That this was a suitable challenge procedure for immunity is assured by the fact that normal mice given a like injection of the virus died with a mortality rate of 80 to 100%. None of the mice developed the disease. Fourteen days later the same mice were given a second intraperitoneal injection of 0.05 ml. of virus and all were still insusceptible to infection.

with 0.1 ml. of the mixture. For virus control, normal salt solution was used in the same manner as the pooled sera. The mixtures were incubated for 2 hours at 37.5° C. refrigerated overnight at 6° C. and then injected intraperitoneally into normal albino mice. The 12 mice injected with a mixture of serum from the resistant mice and virus did not develop the disease, whereas of the 12 mice injected with normal mouse serum or normal saline and virus mixtures, 11 developed paralysis and succumbed.

A summary of the tests for immunity show that 26 days after receiving a single subcutaneous injection of active virus all mice were insusceptible to infection as evi-

denced by failure of intraperitoneal injection of virus to produce the disease. A second and third similar test after 40 and 54 days showed a like result. On the latter day sera from these mice neutralized the virus *in vitro*.

**Summary.** In both estrogen prepared and untreated control mice subcutaneous injection of active poliomyelitis virus, when not resulting in the frank disease, produced subclinical immunity. However, a greater proportion of estrogen treated mice failed to develop the disease and consequently the number of mice that developed subclinical immunity was greater than in the controls. Hence, preparation of the host with estrogenic substance effected a decrease in production of disease by active virus, and an increase in occurrence of subclinical immunization.

These experiments represent an approach to immunization through the use of a new, albeit old, principle whereby

subclinical immunization rather than clinical disease is produced by inoculation of the prepared host with unmodified virus, rather than by the now conventional method of inoculation of the unprepared host with modified or attenuated virus. Even though a procedure such as administration of estrogenic substance would produce an autarcetic state, it might not be feasible to maintain such a state of resistance by its continued use. It might be possible, however, to produce a temporary period of resistance during which subclinical immunity could be safely induced with active virus.

Neither these experiments nor any of the other examples of enhancement of host resistance to experimental infection cited begin to approach present-day standards of safety, though in this respect they are probably all superior to variolation as practiced a century ago.

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## INFLUENZA AT AN ARMY CAMP IN 1945-1946

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DURING the fall of 1945, there was an epidemic of acute respiratory disease at Fort Benjamin Harrison. This epidemic was partly due to the virus of influenza B, as proven by serologic studies, but included cases clinically similar to influenza in which no rise in antibodies against the influenza viruses was found. Furthermore, the epidemic at the army post preceded the nation-wide influenza epidemic by several weeks. The purposes of this paper are: (1) to describe the course of the epidemic at Fort Harrison; (2) to outline a simplified variant of the familiar chick-cell agglutination inhibition test for influenzal antibodies; (3) to discuss the epidemiology of influenza as related to this outbreak; and (4) to discuss certain observations made by us in the course of the epidemic.

**Methods.** (a) STATISTICAL. Statistical studies were based on acute respiratory diseases in general (Collins<sup>3</sup>). The term is here used to include colds, influenza, nasopharyngitis and other common respiratory diseases, as well as pneumonias. Rates are calculated as hospital admissions per 1000 per annum. The data for Fort Harrison were taken directly from the records on the wards; the rates for "U. S. Military" were taken from the Weekly Health Reports published by the Surgeon-General's Office.

(b) LABORATORY. Serologic studies for antibodies against influenza viruses were performed by a virus dilution method of the chicken cell agglutination inhibition test.

*Fresh chicken cells* were washed 3 times, packed and diluted with saline to make a 2% suspension. They were kept in the ice-box and never used after the 3rd day. *Virus* was prepared by inoculating 10 to 11 day eggs, and harvesting the allantoic fluid 2 days

later. The product of each egg was tested for hemagglutinins by allowing a small amount of fluid to mix with the embryo's red cells on the bottom of a Petri dish. The fluids of several eggs were pooled and the product stored in large test tubes at 4° C. *Human sera* were obtained early in the disease, and again 7 to 14 days later from each case.

*Procedure* for the test was as follows: Two-fold dilutions of virus-allantoic fluid in saline were first prepared in large test tubes, ranging in final dilutions from 1:16 to 1:2048. Then, 0.25 ml. of each dilution was added to Kahn tubes which were set in series in large racks. The serum was diluted by adding 0.2 ml. of serum to 3.8 ml. of saline, and to this was added 4 ml. of the 2% chicken cell suspension. The resulting serum-chicken cell combination was thoroughly mixed, and 0.25 ml. added to each Kahn tube with virus. After adequate shaking, the tubes were allowed to stand at room temperature for 1 hour. Tests were read according to the cell sedimentation pattern in the bottom of the tube. The tube was called positive if the pattern was diffuse; negative, if the cells were in a central button which would run when the tube was tipped, and  $\pm$ , if of an intermediate form. The principle of titrations using a constant amount of serum against decreasing quantities of virus was employed by us on occasions in animal neutralization tests. Such a method has the advantage of measuring the effect of antibody on a virus endpoint determined at the time of the serologic test rather than a predetermined virus endpoint which may vary between the time of the original virus titration and the test. A virus dilution method for determining inhibiting antibodies with the use of human type "O" cells was employed by another group of workers.<sup>4</sup>

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Each serum was titrated against the PR8 strain of influenza A virus, and the Saha strain of influenza B virus. (The Lee strain of influenza B was also used in most titrations; results with it were similar to those obtained with Saha virus.) A control without serum was run routinely as a virus titration, and also known positive chicken sera against both influenza A and B were included. The early and late specimens from the same patient were run simultaneously.

The extent of reduction of the hemagglutinating capacity of a virus by the constant dilution of serum (1:80) determined the serum titer which was calculated as the ratio of the greatest dilution of virus *without* serum giving a  $\pm$  reading, to the greatest dilution of virus giving a  $\pm$  reading in the presence of the serum. For example: If the control was  $\pm$  in the 7th tube (virus dilution 1:1024) and the serum-virus was  $\pm$  in the 4th tube (virus dilution 1:128) the titer was 8. Whenever the transition was directly from positive to negative the endpoint was considered to be half-way between the last positive and the first negative tube. Repeated tests by this method gave consistent results. A patient was considered to show serologic evidence of influenza if there was at least a 4-fold rise in titer, on comparing the late with the early specimen.

**COURSE OF THE EPIDEMIC.** The numbers of hospital admissions for common respiratory diseases and pneumonias at Fort Benjamin Harrison from June 1945 to February 1946, by week of admission, are given in Table 1. It will be seen that the hospitalization rate for respiratory diseases from June to mid-September was low. Then, during the 3rd week in September, the rate suddenly rose and continued to rise until it reached a peak in early November. Following this, the rate declined and reached a low level by late December. The epidemic may be described as a distinct peak in the respiratory disease incidence, covering a period of about 15 weeks, with its crest in the 8th week.

The outbreak at Fort Harrison reached its peak and had begun to decline before the morbidity in the U. S. Army began its rise. The available evidence on influ-

enza in Indiana and the U. S. civilian population in general (figures reported by the Indiana State Board of Health, and the U. S. Public Health Service Reports) shows that the sharp rise in the civilian rate came in late November, about the same time as that for the U. S. Army in general. All 3 were about 2 months after the rise in respiratory disease at Fort Harrison.

**CLINICAL STUDIES.** (a) *Cases Showing Definite Evidence of Influenza B.* There were 41 cases which showed serologic evidence of influenza B. The average age was 25 years; only 1 woman was included. Their distribution by age, sex, length of time in service, rank and unit was about that which would be expected with random distribution on the post. On the average, the men had been sick about 2 days before entering the hospital; this was usually because they had tried to "fight it out" before reporting sick. On admission, their commonest complaints were general malaise with muscular aches and with backache (68%), "feverishness" (63%), a sore throat (56%) and headache (56%); 44% had some other complaints such as chest pain on deep inspiration, nausea, diarrhea, dizziness, aches in the eyeballs, anorexia or hoarseness. Disorientation was observed in 1 patient who had been hospitalized several months for non-union of a fracture sustained in combat. The average admission temperature was 101° F., and the average admission pulse 94. The highest temperature noted on any proven case of influenza at any time was 103.6° F.

Physical examination showed most all the patients to have mild prostration, a flushed face, a reddened throat and moderately enlarged tonsils. Coryza and nasopharyngitis were noted in 93%; the pharynx usually showed moderate injection, with the venules engorged but without the extreme reddening often noted in streptococcal sore throat. Cervical adenopathy was present in 22%, a dry cough in 59%. Profuse sweating, which usually came on at night, was observed in 34% of the

cases. Other signs such as conjunctivitis, râles at the lung bases, tonsillitis, epistaxis and extreme prostration were seen in 1 or 2 cases. Complications were rare and unrelated to the disease.

The routine care of the cases was simple. It consisted of bed rest, forced fluids, regular diet, acetylsalicylic acid—acetophenetidin—caffeine tablets for aches, sleeping tablets if desired, neosynephrine nose drops to be taken by the patient 3 or 4 times a day, saline gargles, and elixir of terpene hydrate with codeine for cough. Sulfadiazine or penicillin was given to 10 patients for a brief time with no demonstrable effect. The course of the

acute blood specimens. It will be seen that, except for a single case which will be discussed later, there were no significant changes against influenza A (PR8 strain). In contrast to this, the mean titer against influenza B (Saha strain) rose from 3 in the acute sera to 37.9 in the convalescent sera, a mean rise of 12.9-fold.

(b) *Cases Not Showing Definite Evidence of Influenza.* As stated above, serologic tests were not generally considered significant for influenza unless there was a 4-fold rise in titer of the antibodies. There were 30 influenza suspects who did not show this rise. Of these, 8 showed a 1 tube (2-fold) rise in titer against influenza B

TABLE 1.—COMBINED RATES OF ACUTE RESPIRATORY DISEASES

(Calculated as hospitalizations per 1000 per annum)

Week ending	Ft. Harrison Military rate	U. S. Military rate	Week ending	Ft. Harrison Military rate	U. S. Military rate
June 8 . . .	28	118	Oct. 5 . . .	89	78
15 . . .	30	107	12 . . .	118	91
22 . . .	43	103	19 . . .	173	90
29 . . .	25	101	26 . . .	178	95
July 6 . . .	6	88	Nov. 2 . . .	215	92
13 . . .	34	84	9 . . .	232	96
20 . . .	38	88	16 . . .	189	98
27 . . .	26	86	23 . . .	208	113
Aug. 3 . . .	33	87	30 . . .	140	161
10 . . .	43	85	Dec. 7 . . .	116	182
17 . . .	33	82	14 . . .	40	183
24 . . .	33	91	21 . . .	65	170
31 . . .	29	89	28 . . .	7	158
Sept. 7 . . .	46	79	Jan. 4 . . .	59	171
14 . . .	34	74	11 . . .	29	200
21 . . .	92	80	18 . . .	7	181
28 . . .	101	82	25 . . .	16	195

disease was uneventful in all cases. Assuming that fever began with the onset of symptoms, fever of 99° F. or over lasted from 2 to 8 days, with an average of 5 days. The average hospital stay was 11.6 days, with 6 and 28 days the extremes. Routine laboratory studies revealed the following. The admission white blood count averaged 6317, ranging from 4500 to 10,000. The polymorphonuclears averaged 63.5%, with extremes of 32% and 78%. Beta hemolytic streptococci were identified in 4 of 29 throat cultures. The results of serologic tests on acute and convalescent sera are summarized in Table 2, with Table 3 demonstrating the titer ratios of the convalescent to the

and were considered serologically questionable cases. Analysis of their clinical course shows no significant differences from the definite cases.

There were 22 paired specimens in which not even a 1 tube difference was found. Ten of these had relatively high titers against one or the other of the influenza viruses used in the tests. In 3, this might be explained on the basis of previous vaccination. The mean titers of the 8 questionable cases, and the 22 cases with no antibody rise are shown in Table 4, along with the mean titers of the definite cases of influenza, a group of 29 normal prisoners who had not been vaccinated, and 15 normals who were vaccinated.

(c) *A Case With Serologic Response Against Both A and B Viruses.* One patient showed a strong serologic response to both Type A and Type B influenza viruses. Review of his history showed that he had had malaise, chills, fever and headache on the train while *en route* to Fort Harrison. Several others on the same train had had the same symptoms, and 2 of his close companions from the trip were bled. Both had high titers against

EPIDEMIOLOGY AND GENERAL DISCUSSION. *The Source of the Epidemic.* The source from which influenza B virus reached Fort Harrison was of primary interest. The fact that men were arriving from all parts of the country suggested that it had been imported. Yet careful examination of the cases by units showed that the respiratory disease rate rose at about the same time in the major units on the post. Included were such diversi-

TABLE 2.—SEROLOGIC TESTS FOR INFLUENZA

	Recorded titer														Mean titer
	1*	1.5	2	3	4	6	8	12	16	24	32	48	64	96	
Frequency of titers vs. PR8 virus in 1st specimen	1	11	5	7	4	2	..	..	5	3	1	1	1	..	4.3
Frequency of titers vs. PR8 virus in 2nd specimen	2	7	6	8	3	3	..	1	5	3	1	1	1	..	4.6
Frequency of titers vs. Saha virus in 1st specimen	2	2	13	9†	12	..	..	2	..	1	..	..	..	..	3.0
Frequency of titers vs. Saha virus in 2nd specimen	..	..	..	..	1	..	2 and 2+‡	..	5	..	6 4+	6† 3+	6 3+	2 1+	37.9

\* Titer expressed as the fold reduction of virus activity by a 1:80 dilution of serum based on red cell agglutination-inhibition reaction.

† One set of sera was tested with Lee instead of Saha virus yielding titers of 3 on the 1st and greater than 48 on 2nd specimen.

‡ Number of specimens with titer greater than that expressed.

TABLE 3.—RISE IN ANTIBODY TITER IN CONVALESCENT SERUM SPECIMENS

	Titer ratio															Mean rise
	0.1-0.9	1	1.1-1.9	2	3	4	6	8	11	12	16	21	24	32	48	
Frequency distribution of titer changes to PR8 virus . .	6	29	3	2	..	..	..	..	..	..	1	..	..	..	..	1.1
Frequency distribution of titer changes to Saha virus . .	..	..	..	..	..	6	3	6	3	2	5	3	7	4	2	12.9

TABLE 4.—MEAN TITERS OF VARIOUS GROUPS

Group	Cases	Titer vs. PR8		Titer vs Saha	
		Early	Late	Early	Late
Definite influenza	41	4.3	4.6	3.0	37.9
Questionable influenza	8	3.8	3.5	3.5	7.4
Not proven influenza	22	5.9	5.7	5.2	4.6
Normal prisoners	29	2.5	..	4.7	..
Normals, vaccinated	15	2.0	37.0	4.5	11.9

influenza virus Type A, and 1 gave a story of headache and shaking chills on the train. Although these findings are not conclusive, it is possible that all 3 contracted influenza A before arrival at the post. Still, one must not overlook the possibility of an anamnestic reaction. No other cases of influenza A were found. The man who appears to have been infected by both types of influenza in rapid succession was no sicker than the average case infected with Type B alone.

fied groups as general prisoners, who were closely confined, and new recruits who went to the Indianapolis theaters in great numbers. The appearance of the outbreak on the military reservation earlier than in the civilian population was somewhat analogous to the situation in 1918 (Sydenstricker<sup>5</sup>).

The Commission on Acute Respiratory Diseases<sup>1</sup> suggested that "influenza persists in large populations through sporadic cases and limited outbreaks only to return

in epidemic form when the necessary conditions are present which favor rapid dissemination of the agent." Such a limited outbreak occurred at Camp Atterbury, about 35 miles from Fort Harrison, in May 1945. The Saha strain of influenza B virus was isolated there (Sigel *et al.*<sup>7</sup>) and it was suggested that "although the outbreak referred to may remain an isolated episode, the possibility exists that it may represent the beginning of an epidemic wave of Type B etiology. The situation may parallel the experience of 1943, when an epidemic of influenza Type A was preceded by a localized outbreak of influenza in an army camp, from which Salk, Menke and Francis isolated a Type A virus." It is now suggested that Type B virus persisted in the Indianapolis region through sporadic or inapparent cases from May 1945 until its recognition in epidemic form in the fall of 1945. This suggestion is strengthened by the fact that an isolated interepidemic case of influenza Type B was diagnosed at Fort Harrison in July 1945.

Shope<sup>6</sup> has reviewed the relations between human and swine influenzas. A few swine on Fort Harrison were sick with a respiratory disease and the possibility that the human disease had come from an animal reservoir was investigated. Accordingly, 4 hogs were bled in the early days of their disease, again after they had recovered, and their blood tested. These tests were carried out against PR8, Saha and a British swine strain of influenza virus. No evidence of influenza was found.

*Factors Influencing the Spread of Influenza.* A second major point of interest was the method of spread within the camp. The arrival of many new men on the post was mentioned above. This increase alone does not adequately describe the changes, for there was not only an increase in new men, but an enormous rate of turnover. The onset of the epidemic followed almost immediately after this rapid turnover of personnel began.

Review of the daily temperature at Indianapolis reveals that there was a brief

drop in the temperature at just about the same time as the population and respiratory disease rates began to rise. This cool period was not severe but the drop in temperature might have been a provoking factor in the outbreak. It might have contributed to the spread of the disease by keeping men inside the barracks. Because the men were quartered in large rooms which sometimes held over 100 men, considerable opportunity for contacts was present within each sleeping room. This was accentuated by the turn-over and the natural tendency for men to get acquainted.

The difference between conditions which lead to a high effective contact rate and overcrowding as judged by the distance between beds or spaces at the dining table deserves emphasis. Repeated inspections never revealed beds which were closer than 30 inches, and the places at the mess halls did not seem too crowded. Nevertheless, the increased size of the post population greatly increased respiratory contacts. Movie theaters were crowded. Men swarmed into Indianapolis to see a new town by the only regular means of transport, a bus line. Although some extra vehicles were put on, these were not enough to accommodate all passengers. At the peak hours, every bus was filled to absolute capacity with men from all parts of the camp, who thus spent 45 minutes exchanging respiratory flora. Since the same mess halls had to serve an increased population, they were filled to capacity. In brief, there was a marked increase in the respiratory contacts per man per day both on the post and on trips to Indianapolis, even though regulations of bed space, table space and classroom space were met.

*Factors Leading to the End of the Epidemic.* A third topic of major interest was the factors which led to the decline of the epidemic at Fort Harrison. Probably several factors were responsible. At the peak of the epidemic the hospitalization rate for respiratory disease was 232 per 1000 *per annum*. There were probably

many subclinical or mild cases which were not hospitalized. The influx of new inductees slowed greatly in mid-November, and soon after that the strength declined. At about the same time, soon after the peak of the epidemic, a program for the vaccination of all men on the post, against influenza, was instituted. The response to the B component of the lot of vaccine used at Fort Harrison as measured by tests with the Lee and Saha viruses was not as great as that in soldiers in other posts studied by us. Still the increase in antibody level of the post population resulting from vaccination and from clinical as well as subclinical infections was probably another factor.

*Other Respiratory Diseases.* A situation which favors the spread of one respiratory disease usually favors the spread of others. Yet, bacterial infections were notably scarce at Fort Harrison. No cases of streptococcal or staphylococcal pneumonia were seen; while measles, mumps, German measles and atypical pneumonia were notably rare. There was a barely perceptible increase in pneumococcal pneumonia, but it was impossible to tell whether these were secondary to influenza or not.

As mentioned previously, a number of patients showed no serologic response to the influenza viruses. It may be that they had influenza, but that they either did not form antibodies or that their antibodies were not demonstrated by the test. We doubt that many cases are to be explained on this basis. Walks through the barracks in the evening, or inspection of messes, revealed many men with respiratory infections who did not report to sick call. At first we thought we could distinguish among these a syndrome which we called "scratchy throat" and which seemed milder than influenza, without its generalized aches, with a somewhat longer course, with an incubation period over 4 days, characterized by a red, scratchy throat. Throat cultures, antistreptolysin studies and influenza studies were essentially negative. Later, we found that we

could not distinguish "scratchy throat" from influenza B on clinical grounds. The Commission on Acute Respiratory Diseases<sup>2</sup> also found that there were many cases of acute respiratory disease in which they could not make a specific diagnosis, and used the term ARD for these. In view of the Commission's findings, it is our opinion that "scratchy throat" was a separate entity which was present at the same time as influenza B and that it may have been identical with the disease called ARD by the Commission.

*Relation to Other Outbreaks of Influenza.* The Fort Benjamin Harrison epidemic of influenza B was part of the nation-wide epidemic in the fall and winter of 1945-1946. The authors had an opportunity to study specimens from other stations in the Middle West and found serologic evidence of influenza B in army installations in Indiana, Kentucky, Ohio and Nebraska during the months of November and December.

Although the disease at Fort Harrison was mild and associated with few, if any, complications, the clinical findings indicate that it was similar to the general picture of influenza described by Mote.<sup>6</sup> We are unable to distinguish, on clinical evidence alone, influenza B which we saw in 1945, the influenza A which we saw in 1941 and the syndrome called ARD. These clinical similarities emphasize the need for laboratory studies on acute respiratory disease for accurate diagnosis. Since it appears that widespread epidemics are preceded by scattered outbreaks of influenza in the spring and summer, such laboratory studies would forecast the need for vaccination aimed at general prevention.

**Summary.** Clinical, epidemiologic and laboratory findings showed that there was an epidemic of influenza B at Fort Harrison, Indiana, during the fall of 1945. In addition to serologically proven cases of influenza, a clinically indistinguishable syndrome referred to as ARD was present.

Influenza B was known to be present in this area in the spring of 1945, and it



is suggested that the virus persisted in the region through sporadic or inapparent cases throughout the summer of 1945.

ies be carried out during the interepidemic periods in order to establish the presence of influenza in a region, and to predict the need for vaccination.

It is recommended that virologic stud-

We wish to acknowledge the technical services of Sgt. Glenn Wilson and Miss Beverly Guthner who performed many of the serologic tests, and the cooperation of medical officers at the Station Hospital who graciously showed us patients and the records.

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## ENDOCARDITIS DUE TO TYPE B HEMOPHILUS INFLUENZÆ INVOLVING ONLY THE TRICUSPID VALVE

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THE following case report merits publication because a review of the literature indicates that no other instance of bacterial endocarditis due to Type B *Hemophilus influenzae* has been recorded. The case is of further interest because bacterial vegetations involved only the tricuspid valve.

**Case Report.** U. H. No. 771440. *Present Illness.* V. B., a 17 year old school girl entered the hospital on July 26, 1946, because of a debilitating and febrile illness of unknown etiology. About 3 months previously, she had a gradual onset of weakness, anorexia and increasing fatigability. Shortly thereafter, there was an abrupt onset of sharp pain in the left side of her chest anteriorly, which was associated with chills, fever and drenching sweats. She also had pains in the calves of both legs, and generalized aching of the joints. She was hospitalized elsewhere for 7 weeks, during which time she received penicillin and sulfadiazine. During her stay in the hospital she had 3 episodes of epistaxis. Coincident with this treatment she improved and felt fairly well for 2 weeks after returning home. About this time, the mother of the patient was told that a rough sound over her heart had appeared. She was readmitted to the hospital because of fever, malaise, anorexia, nausea and pain in the right side of the abdomen. She developed pain and swelling over the right ankle. Since the onset of her illness, she had noted some impairment of hearing in the right ear. She was transferred to the University Hospital for further evaluation of her illness. Just prior to entry, giddiness and mild dysuria had appeared. At no time had the patient complained of tender fingers and toes, nor orthopnea and edema. No petechiae had been noted.

*Past History.* According to the mother the patient's past life had been characterized

by the absence of robust health. At the age of 5 or 6 years she had pains in the calves; from ages 8 to 10 she was said to be more "nervous, jumpy and jerky" than any of her 10 siblings. She had had scarlet fever without known complications, rubella, varicella and mumps. Her heart had not been examined since the age of 8.

*Physical Findings.* The patient was fairly well developed, pale, and she appeared acutely ill. The temperature was 101° F.; pulse, 120 per minute; respirations, 24 per minute; and blood pressure, 106/70. The pupils and fundi were normal. There was clotted blood in the right ear canal with an intact membranous tympanum. The pharynx appeared normal. The lung fields were clear. The heart was thought to be enlarged 8 cm. to the left of the midsternal line. There was a harsh systolic murmur in the fourth left intercostal space; no diastolic murmur was heard at this time. The rate increased from 120 to 140 in changing from the lying to the sitting position. A protodiastolic gallop rhythm was noted. The liver and spleen were not palpated; both renal areas were tender. Neither petechiae nor edema were noted. The neurologic examination was within normal limits.

The initial impressions were acute rheumatic endocarditis and renal pain due to sulfadiazine. The latter impression was strengthened by the presence of a sulfadiazine blood level of 2.8 mg. per 100 cc. and sulfonamide crystals in the urine. Therapy with sulfadiazine therapy was discontinued and the crystals were not found in the urine after the first day.

*Laboratory Studies.* Blood examination disclosed a hemoglobin of 11.8 gm., an erythrocyte count of 3,680,000 and a leukocyte count of 9850 cells per c.mm. The differential count showed 89% neutrophils, 10% lymphocytes and 1% monocytes. Further hematologic studies revealed a hyper-

plastic sternal marrow, and histiocytes and undifferentiated reticular cells in the peripheral blood, some of which contained ingested erythrocytes. On the basis of the latter finding the presence of a bacteremia or possibly subacute bacterial endocarditis was suggested.

The leukocyte count varied from 14,450 to 4800 cells per c.mm. On 3 occasions a 4% eosinophilia was recorded. The sedimentation rate was measured at 40 to 91 mm. in 60 minutes (Westergren). Albumin was present but once in 22 examinations of the urine. Sugar was frequently present from a trace to 1+ quantities; the fasting blood sugar was 76 mg. per 100 cc. of blood. The highest urine specific gravity was 1.026.

Repeated blood cultures remained sterile with the exception of the presence of a coagulase negative staphylococcus on 2 occasions. Microorganisms were absent from smears and cultures of pleural fluid removed during the 2nd week. A spinal fluid examination on the 34th day showed normal findings. The Kline reaction of blood serum was negative. A tuberculin (1-100) test and a skin test with the nucleoprotein fraction of streptococcus remained negative. The antistreptolysin titer was 250 units. Agglutinins for brucella, *P. tularensis*, *E. typhosa* and paratyphosa were absent. The capillary fragility test was negative. The blood urea nitrogen was 7 mg. per 100 cc. at the end of the 1st month. A biopsy of the left deltoid muscle showed normal tissue.

Electrocardiograms revealed a first degree heart block. This finding was constant throughout her hospital stay.

On admission a roentgenogram of the chest showed evidence of a right pleural effusion and pneumonia of the right lower lobe, both of which slowly receded and were followed by similar changes on the left side.

*Course.* The temperature followed an erratic pattern. During the 1st month her temperature ranged from normal to 101° F., with rises to 103° F. every 3 to 5 days. These intermittent febrile episodes were associated with chills and exacerbations of the chest pain. At the end of a month of observation the temperature rose to 104° and 105° F. daily and continued to do so until 3 days before death when it returned to normal levels. The blood pressure was at no time elevated; the systolic was usually below 100 and the diastolic below 60 mm.

of Hg. Additional physical findings appeared, which were a palpable spleen, and a low-pitched diastolic murmur heard to the left of the sternum in the fourth intercostal space. Besides exhibiting febrile episodes, accompanied by chest pain, the patient also complained of pain in the abdomen, flank and legs during the last 2 weeks of life. These areas were tender to palpation, as well as various muscles, tendons and bones, even when examined gently.

Shortly after admission to the hospital the patient was given 50,000 units of penicillin intramuscularly every 2 hours, but therapy with penicillin was discontinued within a week. A month later penicillin was administered again, and she received a total of about 10 million units without apparent benefit. When she was not receiving penicillin, she was given 6 gm. of sodium salicylate daily for 33 days. She also received whole blood transfusions, vitamin preparations, ferrous sulphate and sedatives.

Regardless of the treatment, her course became progressively worse. On the 49th hospital day, bilateral ankle clonus was elicited. She became progressively more delirious and finally comatose. On the 62nd day jaundice was noted. The one minute bilirubin test on the blood serum showed 7.9 mg. % with a total of 11.5 mg. Bile was present in the urine. A cephalin flocculation test gave a 4+ reaction in 48 hours. The liver was not palpable. She died suddenly on the 66th day.

*Autopsy.* (21 hours after death.) *Gross Findings.* The body was that of a 17 year old white female 170 cm. in length, weighing an estimated 105 pounds. She was well developed but poorly nourished. Rigor, hypostasis and minimal cyanosis were present; jaundice was marked. There were 15 small petechiæ over the sternal area.

The peritoneal cavity contained 500 cc. of clear amber colored fluid; the right pleural cavity contained 30 cc. and the left 15 cc. of a similar fluid; there were 35 cc. of clear fluid in the pericardial sac. There were fresh pleural and interlobar adhesions on the right.

The heart showed a square milk spot 2 cm. in size over the anterior surface of the right ventricle. The margin of the mitral valve was slightly thickened but was not deformed and did not have vegetations; the chorda tendinæ appeared normal. The valve measured 7 cm. in circumference. The aortic

and pulmonary valves appeared normal. The entire length of the tricuspid valve was occupied by large, yellow, warty vegetations extending a full 18 mm. out from the valve margin. The vegetations extended down the chorda tendineæ and there was one patch on the ventricular endocardium. The auricular endocardium was free of involvement. The heart weighed 275 gm.; no chamber was notably dilated or hypertrophied. The right ventricular wall measured 4 mm. in thickness along the lateral wall and 2.5 mm. at the lower margin. The coronary arteries were normal.

The right *lung* weighed 880 gm., the left 675. There were multiple fine petechiæ over the posterior visceral pleural surfaces of both lungs. There was widespread bilateral pulmonary edema. There were 3 small hemorrhagic areas grossly resembling infarcts (1 in the lower portion of the right upper lobe and 2 in the inferior portion of the left lower lobe). No emboli were seen grossly. Throughout the areas of pulmonary edema there were scattered foci of bronchopneumonia. This was particularly apparent on the left side.

The *spleen* was greatly enlarged, extending well below the costal margin and toward the midline. It weighed 830 gm. No infarcts were identified.

The *liver* weighed 2250 gm. There were no infarcts nor occlusions of the hepatic artery. The liver appeared to be affected by cloudy swelling.

The right *kidney* weighed 100 gm., the left 125. Both capsules stripped easily and the surfaces appeared normal. The lower pole of the right kidney showed an old depressed scar.

The *brain* showed congestion of the vessels.

**MICROSCOPIC EXAMINATION.** *Heart.* The aortic and pulmonary valves were normal. The mitral valve had prominent blood-vessels and an increase in collagen with fibroblastic proliferation in the free edge of the valve. There was no fibrinoid material. The slight thickening noted grossly and the microscopic changes indicated an old rheumatic infection which had not healed completely and which had not caused serious valve deformity. Sections of the tricuspid valve showed the large thrombus composed of platelet masses, polymorphonuclear cells and scattered gram-positive, pleomorphic organisms seen for the most

part as small rods, which were rounded on the ends. There were no microorganisms resembling streptococci or staphylococci. Some areas of the thrombus showed granulation tissue. Underlying the thrombus in the valve itself was considerable fibroblastic proliferation. There were some prominent vessels but no palisade arrangement of cells nor fibrinoid material. The adjacent endocarditis probably accounted for the fibroblasts and dilated vessels; there was no positive microscopic evidence of old or recent rheumatic infection and the conclusion was that the hemophilus infection was the first invasion of this valve. The heart muscle showed a mild diffuse polymorphonuclear myocarditis.

*Lung.* Most of the sections showed some alveoli filled with erythrocytes or precipitated fluid with the alveolar wall disrupted in some regions. Adjacent to these areas there were thrombosed veins and less frequently thrombosed arteries. Adjacent to these areas small arteries and arterioles were seen in all degrees of thrombotic or embolic occlusion; occasional veins were similarly plugged. The corresponding vessel walls were infiltrated with polymorphonuclear cells, sufficient in some instances to be termed an arteritis. The *pleura* was thickened.

*Kidney.* The glomeruli were enlarged and showed considerable endothelial proliferation but blood cells could be seen in the capillaries. The tubules and vessels appeared normal. There were many small collections of lymphocytes particularly near the glomeruli. The conclusion was subclinical acute glomerulonephritis. The sections through the old scar showed complete hyalinization of many glomeruli.

*Bladder:* There was a mild cystitis.

*Liver:* There was a very slight fatty metamorphosis in the cells adjacent to the central veins.

*Spleen:* The red pulp was engorged with erythrocytes. There was an increase in the number of polymorphonuclear cells in the pulp and particularly in the sinusoids. The conclusion was acute splenitis.

*Adrenal:* There were some collections of lymphocytes in the medulla.

*Pancreas:* Sections showed nothing remarkable.

*Brain:* Sections of the brain showed scattered acute inflammatory lesions. In some regions there was a number of neutrophils

throughout the leptomeninges. The conclusion was early suppurative encephalitis.

**BACTERIOLOGIC STUDIES.** At autopsy blood was withdrawn from the right ventricle under sterile precautions. The heart was opened aseptically, smears were prepared from the vegetations, and portions of the vegetations were placed in tryptose phosphate broth. Gram stains of the smears revealed small, gram-negative rods with rounded ends. Similarly staining organisms were obtained from the cultures of heart's blood and from the vegetations. Growth of the organisms took place only in presence of "X" and "V" factors. The organisms failed to grow on the surface of blood agar. However, growth was supported on freshly prepared chocolate agar plates. Growth also took place on blood agar plates adjacent to colonies of coagulase-positive staphylococcus, but without hemolysis around the small, opaque colonies of *H. influenzae*. Organisms from young cultures in broth revealed the presence of capsular swelling when mixed with Type B *H. influenzae* rabbit antiserum. This specific Quellung phenomenon was corroborated in 2 different laboratories.

Although the Gram-Weigert tissue stain showed the organisms in sections of the vegetations to be gram-positive, stained preparations of smears of the vegetations and of the organisms cultured from the heart's blood were consistently gram negative. The dissimilarity between the 2 staining techniques has been noted with other gram-negative organisms.<sup>11</sup>

**Comment.** Influenza bacilli associated with human disease have been divided into 2 main groups, namely, *H. influenzae* and *H. parainfluenzae*. The former requires the so-called "X" and "V" factors for growth, whereas the growth of the latter is supported by only the "V" factor. Furthermore, as Pittman<sup>8</sup> and Platt<sup>9</sup> have shown, smooth, encapsulated strains of *H. influenzae* may be divided into several types with specific antisera. In a review of the reported cases of influenzal endocarditis, Craven, Poston and Orgain<sup>5</sup> have accepted 36 cases, including 2 of their own, as being due to influenza bacilli. But in this group there was not one proved case caused by *H. influenzae*. More recently, Rose<sup>10</sup> reported the clinical and patho-

logic findings of the first authentic case of bacterial endocarditis due to *H. influenzae*. The causative organism was Type A *H. influenzae*.

In the present case, a pure culture of *H. influenzae* was isolated from the vegetations on the tricuspid valve. Growth of this organism took place only in the presence of "X" and "V" factors, and when studied in 2 different laboratories, was found to be *H. influenzae*, Type B. Repeated cultures of venous blood during life remained sterile. There were no demonstrable embolic phenomena while the patient was under observation. The sterile cultures and absent peripheral emboli may be accounted for by the fact that localization of the lesion was on the right side of the heart, and the lungs filtered out the organisms from the blood. It is unfortunate that the bacilli were not isolated from the blood stream during life, since it has been demonstrated that strains of Type B *H. influenzae* are sensitive to the antibacterial action of streptomycin.<sup>2</sup> Cultures of the strain obtained at post-mortem were lost before their *in vitro* sensitivity to streptomycin could be determined. It is of interest that Type B *H. influenzae* is the most frequent cause of meningitis in infants under 12 months of age at the University of Minnesota Hospitals. However, this organism rarely causes serious disease in adults. Alexander,<sup>1</sup> who has had an extensive experience with infections caused by this species of influenza, has never encountered it as a cause of bacterial endocarditis.

Kresky<sup>6</sup> has reported a case of a 3 year old girl who died of suppurative pericarditis due to Type B *H. influenzae*. At autopsy, the endocardium and surfaces of the valves appeared normal. He described 5 other cases collected from the literature, 3 with meningitis. Postmortem examination was carried out in 2 of the 5 cases and no valvular disease was found.

Another pertinent feature of the findings in the present case was the localization of the bacterial vegetations on only the tricuspid valve. Blumer,<sup>3</sup> in a review

of 146 cases of subacute bacterial endocarditis which came to autopsy, stated that the tricuspid valve was the only valve involved in 3 cases (2%). Middleton and Burke<sup>7</sup> found 1 out of 49 cases at the Wisconsin General Hospital with involvement of the tricuspid valve only (2%). In the material studied in the Department of Pathology at University of Minnesota Medical School, Clawson<sup>4</sup> observed localization of vegetations on the tricuspid valve alone in 7 of 363 cases of subacute bacterial endocarditis (1.92%).

There were no features in this patient's illness which, on an etiologic basis, would serve to distinguish the clinical course from that of other cases of subacute bac-

terial endocarditis due to *H. parainfluenzæ*. This is in agreement with the conclusions of Rose<sup>10</sup> with respect to his case of Type A *H. influenzae*. The atypical clinical course may be ascribed in part to the localization of the bacilli on the tricuspid valve.

**Summary.** 1. The clinical and pathologic findings are described for a case of subacute bacterial endocarditis due to Type B *H. influenzae*. As far as can be determined, this is the first proved instance of bacterial endocarditis caused by this species of *influenzæ*.

2. The bacterial vegetations were localized on only the tricuspid valve.

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## STREPTOMYCIN THERAPY OF TULAREMIA IN U. S. ARMY HOSPITALS

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HEILMAN<sup>5</sup> first reported in 1944 that streptomycin exerts a strong *in vitro* action on *Pasteurella tularensis* and is capable of curing the experimentally produced disease. This action was subsequently confirmed by us.<sup>8</sup> The first report of its clinical use in tularemia was by Foshay,<sup>3</sup> who reported that after its administration<sup>6</sup> patients with infection of the ulceroglandular type all showed subjective improvement, regression of lymphadenitis, and remission of temperature. Other reports were to the same effect.<sup>1,2,4,6</sup> The National Research Council's most recent report<sup>7</sup> on streptomycin in the treatment of infections included 67 cases of tularemia with 63 recoveries, on the basis of which the following statement was made: "It can be stated with confidence that streptomycin is an extremely effective agent in tularemia and that it is by far the best therapeutic agent available for the treatment of this disease. Early diagnosis and treatment by intramuscular injection for 5 to 7 days with an average amount of 1 gm. daily should be used in all patients. In the pulmonary and pleural forms with continuous fever without localizing signs, it is desirable to give 2 gm. daily for 7 days or longer until the disease is under control."

Present experience in the Army Streptomycin Study program covers 10 cases of tularemia, 1 of the typhoidal and the others of the glandular type. Pneumonia was a complication in 3 cases, in 1 of which it was associated with nephritis. The patients, who were all adult males, acquired the infection in the South or Southwest of the United States. Two patients had had recent contact with wild rabbits and 4 presented tick bites at the site of the local lesion. In the 2 remain-

ing cases the history of contact was obscure. All patients had, or later developed, specific agglutinins in high titer, but the causative agent was isolated from only 2 patients.

Streptomycin was administered to all patients intramuscularly at intervals of 3 or 4 hours in daily doses of 1 to 3 gm. for periods of 7 to 14 days. Recovery was smooth in all cases, without relapses or complications.

REPORT OF CASES. CASE 1. *Typhoidal type*. A white male, 32 years of age, who had killed and dressed wild rabbits a week earlier, suddenly developed headache, generalized aching, chills, fever and stiff neck. The patient's brother-in-law who also helped dress the same rabbits was admitted to another hospital because of an ulcer on his finger and a diagnosis of "rabbit fever." On admission the temperature was 104.5° F. with extreme nuchal rigidity, suggestive Babinski and Kernig signs. No localized swelling or tenderness was evident on examination. The abdomen, heart, and lungs were clinically negative. The spinal fluid was negative. The white blood count was 11,700 (77% polys with 10% stab cells). The admission chest film was negative. On the basis of the above findings, a tentative diagnosis of tularemia, typhoidal type, was made. The day after he was hospitalized, which was the 8th day of illness, blood serum agglutinins for *P. tularensis* were positive in a dilution of 1:40. Roentgenologic examination confirmed the presence of a right lower lobar pneumonia, but no causal organism could be grown from the sputum.

Streptomycin was administered in doses of 0.125 gm. intramuscularly every 3 hours. The temperature promptly fell from 105° F. to normal, the fall being followed by a secondary rise to 100° F. At the end of 48 hours, because of temporary exhaustion of the supply, the drug was discontinued for





every 3 hours and was continued for 15 days. A total of 30 gm. was given. The ulcer improved rapidly, and was healed in 7 days. The cervical lymph nodes became fluctuant and required incision and drainage. Cultures on cystine media of material taken from lymph nodes were negative, as were cultures of the ulcer taken before streptomycin was begun. The illness was complicated by a right lower lobar pneumonia, presumably of tularemic origin, since no other etiologic organism could be grown. Fever subsided by lysis on the 35th day (Fig. 1). In the meantime the pneumonia cleared, and drainage from the lymph nodes ceased with recession of the swelling, and uncomplicated wound healing.

**CASE 4. Oculoglandular type.** A white male, 26 years of age, was admitted with a history of having rubbed the left eye after scratching the site of a tick bite on the lower extremity, about a week prior to admission. Four days before entering the hospital the eye became swollen, red, itchy and painful. Examination revealed a swollen, tender, left eye with a marked conjunctivitis. There were 2 opposing ulcers of the conjunctiva of the lower lid each measuring approximately 3 mm. in diameter. There was considerable marginal hyperemia and some purulent exudate in the vicinity of the ulcers. A string of small, lymph nodes presented in the anterior cervical chain, and the largest measured approximately 1 cm. in diameter. Smear from the conjunctival ulceration showed small gram-negative rod-like organisms morphologically resembling *P. tularensis*. On admission the temperature was 103° F. Blood serum agglutination for *P. tularensis*: day of admission, negative; at the conclusion of therapy, positive, 1:80; 1 week after cessation of therapy, negative. Urinalysis, complete blood count and blood serologic tests were non-contributory. A diagnosis of oculoglandular tularemia was made. The patient was given streptomycin, 0.4 gm. intramuscularly every 3 hours for 12 days, and in addition, topical applications of streptomycin, in sterile isotonic saline, 3 mg. per cc. 4 to 8 drops 4 times a day. The acute inflammatory process subsided rapidly. On the 9th day of treatment the eye appeared normal, the ulcerations were healed, the vision of the left eye was 20/30. At the time of discharge, 1 week later, recheck of the vision showed 20/20 readings.

**Comment.** In Case 1 the dramatic, immediate response to streptomycin was not maintained because lack of supply caused an interruption in continuity of administration of the drug. Cure was effected when a second course was given, and the drug assuredly influenced the result. In Case 2 streptomycin therapy, while not dramatic in effect, undoubtedly played a rôle in the patient's recovery; the severity of his illness would ordinarily have been associated with a grave prognosis. In Case 3 the patient had passed the critical stage of his illness when streptomycin therapy was begun, and the only objective evidence of therapeutic effect was the healing of the ulcer focus and the recession of the lymphadenopathy. In Case 4 streptomycin therapy effected a rapid cure. The conjunctivitis and associated ulcers healed within 9 days, and the vision in this eye was normal at the conclusion of the course of therapy.

The remaining 6 cases are not presented in detail because they contain no particular features of interest. In these cases the disease was of the ulceroglandular type and diagnosis was made by positive agglutination tests in dilutions of 1:1280 to 1:5120. Each patient had 7 gm. or more of streptomycin over a 7 day period. Healing of the initial lesion, in each case in the groin, was slow but progressive, and regression of the associated lymphadenopathy was also progressive. In 3 instances suppuration of the lymph nodes was extensive enough to require aspirations. With streptomycin therapy wound healing will follow surgery.

The combined experience of all observers indicates that streptomycin is the most effective drug presently available for the treatment of tularemia. Given in doses of 1 to 3 gm. daily it causes remission of the local and systemic manifestations of the disease. A dosage in the amount of 2 gm. daily appears preferable and is recommended. Duration of treatment varies from 7 to 14 days, depending upon the type and severity of the infection. In the later stages of the ulcero-glandular

form of the disease, the rôle of streptomycin therapy is less significant, since (1) spontaneous cures are known to occur, and (2) the observed changes in our series of cases were slow.

**Summary and Conclusions.** 1. Streptomycin is the most effective drug available for the treatment of tularemia. Employed in doses of 1 to 3 gm. a day, the antibiotic produces remission of the local and systemic manifestations of the disease.

A 2 gm. a day dosage schedule appears preferable and is recommended. Duration of treatment varies from 7 to 14 days, depending upon the type and severity of the infection.

2. Experiences with 10 cases of tularemia treated with streptomycin in U. S. Army hospitals are presented.

3. Accidentally or deliberately incised or excised buboes of tularemia heal with adequate streptomycin therapy.

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## FURTHER OBSERVATIONS ON POLIOMYELITIS IN PREGNANCY

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IN 1945 Fox and Sennett<sup>3</sup> summarized the literature and analyzed the clinical data showing increased susceptibility to poliomyelitis. They recognized a total of 85 cases up to and including the epidemic of 1943. It is apparent that not all cases of poliomyelitis in pregnant women were recorded in the medical literature or in-

to the South View Isolation Hospital, 6 (60%) of whom were pregnant. These patients were in various stages of pregnancy: 3 in the first trimester, 1 in the second, 1 in the third and 1 patient who delivered only 5 days previous to the onset of the disease. In the 1946 epidemic, 14 married women were admitted to the

TABLE 1.—DATA ON 14 CASES IN 1945 AND 1946

Patient	Age	Duration of pregnancy	Convalescence 1945	Result of pregnancy
1. Mrs. N. McF.	35	1½ mos. pregnant	Slight stiffness of neck and back persisted	Expelled blood and products of conception on 3rd to 5th hosp. day
2. Mrs. J. O'C.	19	2 " "	Muscle weakness persisted	Miscarriage ? mo.
3. Mrs. F. L.	38	3 " "	Recovery of muscle spasm and paralysis	Delivered normal baby
4. Mrs. A. K.	25	5 " "	Paralysis of lower limbs	Pt. delivered by Cesarean section but baby died due to Rh factor
5. Mrs. L. K.	30	8½ " "	Died 9 days postpartum	Delivered normal 6 lb. 1 oz. boy
6. Mrs. M. R.	27	5 days postpartum	Died 12 days postpartum	Normal baby
1946				
1. Mrs. W. L.	21	1 mo. pregnant	Marked paralysis (in Emerson respirator at time)	Aborted 1 mo.
2. Mrs. C. E.	23	3 mos. pregnant	Complete recovery	Miscarriage at 3 mos.
3. Mrs. E. B.	31	3½ " "	Recovery of all muscles	Subsequently delivered normal baby
4. Mrs. D. S.	26	3½ " "	Recovery of all symptoms	Subsequently delivered normal baby
5. Mrs. J. E.	27	5 " "	Residual paresis	Miscarriage 3½ mos.
6. Mrs. M. A.	27	6 " "	Complete recovery	Normal delivery
7. Mrs. E. T.	22	7½ " "	Weakness of muscles involved; persisted with little change	Delivered normal baby
8. Mrs. N. P.	23	14 days postpartum	Slight spasm of neck with pain in back muscle and pain of quadriceps	Normal baby

cluded in the paper by Fox and Sennett.<sup>3</sup> Since it seems important to establish thoroughly whether any true relationship exists between poliomyelitis and the pregnant state, we are presenting additional information in this paper.

Data from the 1945 and 1946 epidemics are listed in Table 1. In the 1945 epidemic, 10 married women were admitted

Hospital. Of these, 8 (57.1%) were pregnant. Two patients were in the first trimester, 4 in the second, and 1 in the third. One patient had delivered a normal child 14 days previously.

Thus there seems to be no preponderance of patients in any one of the pregnancy trimesters. Waaler<sup>16</sup> also had found no time relationships as far as inci-

dence is concerned, but he did cite the fact that "the prognosis for mothers contracting poliomyelitis in the last months of pregnancy is bad," since 8 of his 33 patients died in the last two trimesters. Of our 24 cases, 2 died in the last two trimesters. Aycock<sup>1</sup> states that there are fewer cases in the first 2 months of pregnancy, and also concludes from his data "that there is a tendency for the disease to occur in the first trimester in those who are carrying a female fetus." Certainly, additional data would be welcome from further sources to support this interesting observation.

In attempting to summarize the total number of cases of pregnancy complicating poliomyelitis, or of poliomyelitis complicating pregnancy, one is struck by the relative paucity of recorded literature on the subject. The discussion regarding intrauterine poliomyelitis has brought to light several instances of pregnancy complicated by poliomyelitis. While the majority of the authors were primarily concerned as to whether poliomyelitis in the mother has an effect on the fetus, all the cases cited in these reports can be included in the present tabulation. These papers, however, furnish no comparative data as to the incidence of the disease in gravid *versus* non-gravid women, which is a very important consideration. Harmon and Hoyne<sup>6</sup> cite 2 women, aged 30 and 32 years respectively, who were in the 6th and 8th months of gestation. Wakefield<sup>17</sup> reported 1 woman 18 years of age who developed poliomyelitis during the 12th week of pregnancy. Subsequently, she delivered uneventfully a normal child at 8½ months. The report by Waaler,<sup>16</sup> on various aspects of the problem, cites 33 cases of poliomyelitis in women in different stages of pregnancy. He also notes that in the Bergen, Norway, epidemic of 1941, the Epidemiologic Department of the Haukeland Hospital had 23 women, 7 of whom were pregnant. Netteblad<sup>12</sup> quoted 6 cases out of 42 adult women. Jacobsen<sup>9</sup> observed 7 pregnant women with poliomyelitis and Palmsti-

erna<sup>13</sup> had 2 cases of poliomyelitis in mother and new-born infant. Hürny<sup>8</sup> mentioned 2 cases and Schultze,<sup>15</sup> Zimmermann,<sup>18</sup> Guttman,<sup>4</sup> Ruhl,<sup>14</sup> Hansen,<sup>5</sup> and Morrow and Luria<sup>11</sup> mentioned 1 case each. Waaler<sup>16</sup> claims to have succeeded in finding only 25 cases of poliomyelitis in pregnant women in the literature. He was obviously handicapped in his search for the American literature was evidently unavailable to him. In our judgment, the literature shows a total of 71 cases of pregnancy with poliomyelitis. An accurate diagnosis is essential in any consideration of the subject. Without complete verification, cases not poliomyelitis could pass as such.

We wish to refer now to an interesting illustrative case.

CASE 1.—A 27 year old white female was admitted to the South View Isolation Hospital, having had a normal spontaneous delivery of a live and healthy baby girl. During her labor she suddenly developed dizziness and presented a right hemiplegia with inactive right diaphragm, and a flaccid paralysis of the right arm and leg. She became increasingly worse and was admitted to the Hospital as a poliomyelitis suspect 4 days later.

*Physical examination* revealed a well-developed and well-nourished white female who had a paralyzed right arm and leg, pain and tenderness in the right shoulder and arm, absent knee jerks bilaterally, and marked weakness of the left arm and left leg. Her respirations were labored and she was unable to void. A catheterized specimen of urine was cloudy and contained 4+ albumin and numerous pus cells. Spinal puncture released fluid which contained 150 RBC per c.mm. and 15 WBC per c.mm. Two days later the spinal fluid contained 274 RBC per c.mm. and 2 WBC per c.mm. Her temperature remained elevated, varying between 99.6° and 105° F. Examination on September 12 revealed a completed flaccid paralysis of the right arm and right leg, right sternocleidomastoid, and right diaphragm. She was barely able to move the fingers of her left hand and the toes of her left foot. The left diaphragm was active, but the right side of the chest was entirely

inactive. Cough reflex was present but weak, and her ability to swallow at this time appeared to be unimpaired. The bladder did not function and required catheterization. Two days later she developed increasing difficulty in swallowing and did not respond to questions. The mucus collecting in her pharynx had to be aspirated frequently and she continued a progressively downward course, finally becoming moribund. Death occurred on Sept. 16, 1945.

*Necropsy.* The following significant lesions were found in the brain and spinal cord. The medulla showed a gray-pink discoloration of the posterior one-third of the floor of the fourth ventricle; the right side was frankly hemorrhagic. The serial sections throughout the medulla and cervical cord showed that the hemorrhage formed a continuous columnar structure extending well into the upper portion of the cervical cord. The hemorrhagic area was located in the right side of the cord and involved primarily the right anterior column. Microscopic examination revealed an irregular area of hemorrhage and softening in the right ventral area. The hemorrhage destroyed the tissues in this area while the surrounding zone was vacuolated, congested, and exhibited neuron degeneration. The anterior horn cells throughout the lumbar and thoracic cord were without significant change. The postmortem conclusions were that this was a case of hematomyelia complicating labor.

The interesting point about this case is the ease with which it could be misdiagnosed as a case of acute anterior poliomyelitis, were it not for the necropsy and spinal fluid findings.

The case cited above may be compared to one of poliomyelitis.

**CASE 2.** A 30 year old woman, pregnant  $8\frac{1}{2}$  months, entered South View Isolation Hospital on Nov. 11, 1945, with complaints of pain in the back of the neck and along the back of the thighs and lower back. Temperature on admission was  $98.8^{\circ}$  F., pulse 132, respirations 26. Reflexes were 0 to 1+ with flaccid paralysis of both lower extremities, flaccid paralysis of the right arm, and weakness of the left arm. This patient was able to swallow without too much difficulty but developed slight occasional twitching at the left angle of the mouth on the 2nd hospi-

tal day. On the 3rd day, she gave birth to a 6 pound 1 ounce boy who was and who has remained normal in every respect. The patient's left arm became progressively weaker and by the 6th hospital day she had paraplegia with increased bulbar involvement. She could protrude her tongue only slightly, could open her mouth about 1 inch, and had profound weakness of the facial muscles, especially on the left side. On the evening of the 8th hospital day, the patient had increasing difficulty swallowing as well as a rise in temperature to  $100.2^{\circ}$  F. The course was unchanged until the 12th hospital day when she had very shallow respirations, a rise in temperature, and a fall in blood pressure. The cough reflex disappeared and the patient died that evening.

Laboratory findings showed the spinal fluid clear on admission: 20 cells with 100% lymphocytes. The urinalysis was negative throughout the hospital stay until the day of death when it showed a 4+ albumin, 15 WBC per low-power field and 10 RBC, and an occasional cast.

Treatment included hot packs to the affected limbs and symptomatic medication.

*Autopsy.* Pertinent findings were limited mainly to the brain and spinal cord. These confirmed the clinical diagnosis of poliomyelitis. A focal hemorrhage of the substantia nigra, minute hemorrhages in the cervical cord, pulmonary congestion, basal atelectasis, and an area of myocardial degeneration were also noted.

These 2 cases are presented for comparative purposes to point out the fallacy of regarding a case of paralysis as poliomyelitis merely because it occurs during the epidemic season, when no other cause can be ascertained at the moment.

It is of some interest to note that both grossly and microscopically this case exhibited multiple hemorrhages. So far as we can determine, this occurrence has not been noted in the pathologic changes of poliomyelitis.

**Discussion.** It seems from our data, as from several reports on the subject, that the pregnant woman is apparently more susceptible to the poliomyelitis virus than the non-pregnant woman. The previous paper by Fox and Sennett<sup>3</sup> cited several reports in the literature which supported

the thesis that the endocrine glands influence susceptibility or resistance in some way as yet not fully understood. Numerous references can be made to glandular changes which occur in pregnancy, and, as pregnancy progresses, to the effect of the fetal ductless glands on the maternal metabolism; but more specific citations can be made. The theory that the endocrine glands can influence susceptibility to poliomyelitis receives support from Jungeblut and Engle,<sup>10</sup> who believe that immunity in this disease is dependent upon physique and physiologic mechanisms such as menstruation and pregnancy. However, their work, indicating that the immune body content of the sera varied with the menstrual cycle, has been opposed by the more extensive studies of Hudson, Lennethe and King.<sup>7</sup> Jungeblut and Engle<sup>10</sup> found that after adrenalectomy the sera of certain monkeys failed to neutralize the virus. After treatment with cortical hormone, the neutralizing power returned. Adrenalectomy caused the disappearance of the natural poliomyelitis antibody, but the antibody present in animals recovered from the infection did not disappear. For such cases, Aycock<sup>2</sup> introduced the term "autarcesis," the power to resist infection. This quality is inherent in the normal physiologic function of the body. While he admits that immunity following contact with the virus is important, he stresses the rôle of normally changing physiologic imbalance in causing increased susceptibility to infection. The multiple physiologic changes occurring in pregnancy make it seem not unlikely that differences in susceptibility are encountered between the gravid and

non-gravid state, which make the gravid patient more susceptible.

Several groups of workers have attempted to determine whether poliomyelitis runs an unusually fatal course during pregnancy, but the evidence cannot be regarded as conclusive. Others have presented evidence that the prognosis is bad for mothers contracting poliomyelitis in the last trimester. This issue also cannot be determined with any finality when we take into consideration that viruses with different characteristics make their appearance during one epidemic and in various parts of the country. The variations from year to year and variations in virulence of the virus are only a few considerations to be kept in mind in a critical evaluation of this matter.

**Summary and Conclusions.** 1. The total number of recorded instances in which pregnancy complicated poliomyelitis or poliomyelitis complicated pregnancy is well over 175.

2. Data from the 1945 and 1946 epidemics indicate that of 24 married women admitted to the South View Isolation Hospital with a diagnosis of poliomyelitis, 14 were pregnant.

3. The incidence of poliomyelitis appears to be greater in pregnant than in non-pregnant women, though it has not been feasible to confirm our data by statistical methods.

4. One case of hematomyelia is cited which clinically simulated poliomyelitis.

5. Influence of the glandular changes of pregnancy which affect the physiologic balance of the patient and, therefore, susceptibility to poliomyelitis, is offered as a possible explanation for the apparently greater incidence in pregnant women.

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## PA-PIN (TRANSIENT PARALYSIS) COMPLICATING ASIATIC CHOLERA

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ONE of the authors (Huang<sup>7</sup>) reported 12 cases of Pa-Pin, or transient paralysis, simulating familial periodic paralysis. All of these cases showed a uniform clinical picture identical with that of familial periodic paralysis except for 2 points: (1) absence of family history and (2) frequency of the disease in certain salt-producing areas, where the salt was proved to contain high percentage of barium chloride (as high as 25.69% has been recorded).

Du and Dung<sup>5</sup> reproduced a similar symptom-complex in dogs by oral or intraperitoneal administration of pure barium chloride, and believed barium poisoning to be the cause of the transient paralysis.

One of the authors (Huang<sup>8</sup>) was able to produce similar flaccid paralysis of legs of rabbits by intravenous administration of pure barium chloride, but was not able to abolish the paralysis by intravenous application of potassium as in the human cases. Chow<sup>3</sup> repeated it on dogs with the same result.

Chang and Loo<sup>2</sup> reported a case of poisoning with barium due to ingestion of pure barium chloride by mistake. Not only the symptoms and signs were identical with those of Pa-Pin, reported by Huang, and those of familial periodic paralysis, but also the response to administration of potassium was identical.

Except for Huang's failure in using potassium to relieve paralysis caused by barium in rabbits and Chow's similar experience in dogs, all of the evidence on hand speaks for barium chloride as the cause of the fairly common disease, Pa-Pin, in Szechuan Province. The mechanism of production of flaccid paralysis by barium chloride is not known yet. The cases we are reporting may contribute something

to the understanding of the metabolism of barium in the human body and the pathogenesis of paralysis.

**Case Reports.** The authors met 11 cases of the same transient paralysis among 1620 cases of Asiatic cholera admitted to the Provincial Institute during an epidemic in the summer of 1945.✓ All of the cases developed paralysis immediately after recovery from cholera and all responded to treatment with potassium. The diet given in the Institute during the epidemic was absolutely devoid of free salt and no food from outside was allowed. Different samples of sodium chloride used for intravenous infusion were analyzed by Professor Chow\* and found to contain no trace of barium. The details of the cases are presented in Table 1 in simplified form.

**Discussion.** Aitken, Allot, Castleden and Walker<sup>1</sup> found that, in cases of familial periodic paralysis, both serum potassium and urine potassium were reduced during an attack, and serum potassium returned to normal level and urine potassium was increased above normal after an attack. Unfortunately, determination of serum potassium was not made in the cases of transient paralysis, owing to the lack of facilities for accurate analysis under wartime conditions in China. Judging from the clinical features and good response to potassium, the pathogenesis of paralysis should be the same as that of familial periodic paralysis. If so, it is natural to think that barium exerts its action by disturbing potassium metabolism. Naturally, the question arises: whether familial periodic paralysis is also due to barium poisoning or whether barium poisoning is only one of the causes for disturbed potassium metabolism. Feng<sup>6</sup> showed that

\* Professor Chow used the colorimetric method as described in his article (Chow, C., and Chin, Y. G. Chinese Med. J., 61, 113, 1943).



HUANG, MAO: PA-PIN (TRANSIENT PARALYSIS)

TABLE 1.—DATA OF 11 CASES OF PA-PIN\*

Case No.	Age	Sex	Duration of disease on admission	Main symptoms and signs of cholera					Total amount of normal saline given intravenously (liters)	Appearance of paralysis (time)		Differential blood counts (shortly after onset of paralysis)				Treatment (total amount of KCl given intravenously)	Course
				Vomiting	Diarrhea	Abdominal cramp	Hoarseness	Dehydration		Day of admission	Day of recovery	Red blood cells	Leukocytes	Neutrophils	Lymphocytes		
1	41	M	20	++	+++	Pres.	Pres.	Marked	11	5	1	Not done	Not done	Not done	Not done	2% sol. 415 cc. in 3 doses	Dramatically impr. after KCl injection; compl. recov. in 24 hrs.
2	38	M	10	+++	+++	Pres.	Abs.	Marked	12	7	2	Not done	Not done	Not done	Not done	2% sol. 550 cc. in 2 doses	Dramatically impr. after KCl; compl. recov. in 3 days
3	39	F	24	++	+++	Pres.	Abs.	Marked	16	6	2	Not done	Not done	Not done	Not done	3% sol. 450 cc. in 2 doses	Markedly impr. after KCl; compl. recov. in 10 hrs.
4	20	F	12	++	+++	Pres.	Abs.	Marked	19	5	1	Not done	Not done	Not done	Not done	3% sol. 250 cc. in 1 dose	Dramatically impr. after KCl; compl. recov. in 10 hrs.
5	40	M	24	++	+++	Pres.	Abs.	Marked	9	3	1	Not done	Not done	Not done	Not done	3% sol. 100 cc. in 1 dose	Sudden death after 100 cc. of 3% KCl
6	16	M	12	++	+++	Pres.	Abs.	Marked	15	6	2	5.07	12.0	83	17	3% sol. 250 cc. in 1 dose	Mod. impr. after KCl; compl. recov. in 30 hrs.
7	70	M	20	+	+++	Pres.	Abs.	Mod.	20	5	1	4.30	12.0	91	9	Refused treatment	Disch. against advice; no further information
8	30	F	10	++	+++	Pres.	Abs.	Mod.	2	2	1	3.85	10.3	91	10	After 100 cc. of 3% sol. patient refused treatment because of pain	Mod. impr. after KCl; compl. recov. in 3 days
9	19	M	48	++	+++	Pres.	Abs.	Mod.	9	4	1	5.79	20.8	83	17	3% sol. 500 cc. in 2 doses	Mod. impr. after KCl; compl. recov. in 2 days
10	25	M	20	+	+++	Pres.	Abs.	Mod.	15	6	1	5.38	11.4	80	11	3% sol. 250 cc. in 1 dose	Dramatically impr. after KCl; compl. recov. in 3 hrs.
11	55	M	20	++	+++	Pres.	Abs.	Mod.	23	9	2	3.76	21.8	95	5	3% sol. 250 cc. in 1 dose	Dramatically impr. after KCl; compl. recov. in 3 hrs.

\* All patients were Chinese. None gave history of previous transient paralytic attack. After paralysis appeared all patients showed complete flaccid paralysis of neck and extremities; tendon reflexes and muscular tonicity lost; no sensory disturbance; heart action slow and weak, except in Case 2 where heart action was normal. Food taken during hospitalization consisted of soy bean milk, rice water and powdered arrowroot in all cases. N... food from outside.

barium chloride bears a striking resemblance to eserine in its action on the motor nerve endings of the frog which is just the opposite to our clinical experience. Certainly it requires a good deal of further study to reconcile the apparent contradiction.

No textbooks of medicine<sup>3,10,11</sup> have ever mentioned Pa-Pin or transient paralysis as a complication of Asiatic cholera. This implies that some additional factor must be at play to give rise to such a manifestation. The fact that it displays an identical clinical picture with that occurring simultaneously speaks strongly for a common causation, and its late onset at the time of recovery from gastro-intestinal symptoms after several days' salt-free diet, with no drugs, except non-barium containing saline infusions, would apparently exclude barium as the responsible factor. However, Kunowski<sup>9</sup> has demonstrated barium in human bone and it would not be illogical to ask whether dehydration and acidosis might not mobilize the deposited barium from bones to cause acute manifesta-

tations as in cases of chronic lead poisoning. Dehydration in our cases may have another effect in precipitating symptoms, as Wiley and Wiley<sup>12</sup> have shown that in marked dehydration (5% of body weight) plasma electrolytes (NaCl) and later KCl from the tissue are sacrificed. The marked dehydration here probably has a 2-fold effect upon the potassium metabolism: (1) mobilizing barium to disturb potassium equilibrium, (2) causing loss of potassium from tissue. The two effects together precipitate the clinical symptoms.

**Summary.** 1. Pa-Pin or transient paralysis in Szechuan, a disease showing an identical clinical symptom complex with familial periodic paralysis and most likely caused by ingestion of barium-contaminated salt, is reviewed.

2. Eleven such cases complicating Asiatic cholera are reported. Asiatic cholera as a cause of Pa-Pin has apparently not been previously reported.

3. The mechanism of paralysis production is discussed.

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## THE RELATIVE TOXICITY OF ATROPINE AND NOVATRINE IN MAN

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In the search for a drug possessing an action similar to that of atropine on the autonomic nervous system but which, nevertheless, would be free of its toxic effects, novatriner\* was introduced into clinical medicine.<sup>2</sup> Quigley,<sup>4</sup> using unanesthetized dogs, found the dosage ratio of novatriner and atropine for comparable inhibition of gastric motility to be approximately 1.5:1, while the ratio for the colon was approximately 6:1. The same author<sup>5</sup> also noted inhibition of gastric motility by novatriner in normal men. More recently Martin and Batterman<sup>3</sup> found novatriner to be suitable for reducing the tone and motility of the gastrointestinal tract during abdominal surgery under various anesthetics. Batterman and Rose<sup>1</sup> studied the influence of simultaneous aluminum hydroxide therapy on the absorption of novatriner using visual disturbances and dryness of the mucous membranes as evidence of absorption. Their results indicated that the aluminum hydroxide did not affect absorption and that doses of 60 to 150 mg. of novatriner were necessary to cause mild to marked toxic effects. At the time the present investigation was undertaken, there had not been any carefully controlled study of the toxic manifestation of novatriner as compared to those of atropine, nor has any such comparison appeared since. The purpose of the present investigation was to make such a comparison.

**Method.** The drugs were administered orally to 17 volunteers, 10 of whom were normal medical students, and 7, patients convalescent from minor ailments on the wards of Bellevue Hospital. The ages

ranged from 23 to 50. There were 15 males and 2 females. All observations were carried out in a room or ward in which the illumination was constant. The subjects were kept at bed rest for a period of at least 20 minutes during which time observations were made of the pulse rate, pupillary size and reaction, oral secretions and mental status (dizziness, lightheadedness, tinnitus and teichopsia). Following this control period, the drug was administered and similar observations were made every few minutes for a period of 1½ to 3 hours and then at greater intervals for the remainder of the day. A definite change in any of the symptoms or observed signs was considered as evidence of toxicity. In 15 cases, increasing doses of the drugs were given on successive days in the attempt to reach the point of minor toxicity. Such a procedure would incidentally be of value in the detection of a cumulative action of novatriner.

**Results, and Discussion** The results are summarized in Table 1. The problem under investigation was to determine the minimal toxic dose of novatriner as compared to that of atropine, without reference to the use of this drug in any particular clinical condition. Therefore, essentially normal persons were employed as subjects. In the normal human being, however it is extremely difficult to distinguish between full physiologic effects and minor toxic symptoms of atropine and its congeners. Consequently, though it was appreciated fully that some of the criteria for minor toxicity might really represent full physiologic effects, the first definite changes in heart rate, pupillary size, oral secretions and mental status were considered evidences of minor toxicity.

\* Formerly known as novatropine. For complete description see New and Non-Official Remedies American Medical Association, Chicago, p. 315, 1916.

TABLE 1.—COMPARATIVE TOXICITY OF ATROPINE SULPHATE AND NOVATRINE

TABLE I.—COMPARATIVE TOXICITY OF ATROPINE SULPHATE AND NOVATRINE															
Case No.	Age	Sex	Wt. (kg.)	Diagnosis	Atropine sulphate				Novatrine				Ratio		
					Dose (mg.)	Tachycardia	Mydriasis	Oral secretions	Mental	Dose (mg.)	Tachycardia	Mydriasis		Oral secretions	Mental
1	25	M	66	N	2.60	++	++	++	+	0	27.0	0	0	0	1->10
2	25	M	55	N	2.60	++	++	++	++	+	32.5	0	0	0	1->12.4
3	25	M	75	N	2.13	++	++	++	++	+	27.0	0	0	0	1->10
4	26	M	77	N	2.13	++	++	++	++	+	32.5	0	0	0	1->15
5	25	M	66	N	2.13	++	++	++	++	+	27.0	0	0	0	1->13
6	22	M	61	N	2.60	++	++	++	++	+	54.0	0	0	0	1->25
7	26	M	75	N	2.13	++	++	++	++	+	68.0	0	0	0	1->32
8	23	M	66	N	2.13	++	++	++	++	+	88.0	0	0	0	1->40
9	25	F	57	N	2.60	++	++	++	++	+	68.0	0	0	0	1->32
10	25	F	70	N	2.13	++	++	++	++	+	50.0	0	0	0	1->38
11	45	F	73	N	1.30	++	++	++	++	+	273.0	++	++	++	1->84
12	50	M	66	N	3.25	0	0	0	0	0	90.0	0	0	0	1-45
13	23	M	51	Enteritis	2.15	0	0	0	0	0	220.0	0	0	0	1-67.7
14	45	M	59	Mucous colitis	3.25	0	0	0	0	0	150.0	0	0	0	1->62
15	38	M	73	Renal calculus	2.60	++	++	++	++	+	180.0	0	0	0	1-50
16	40	M	59	Cholecystitis	2.60	++	++	++	++	+	120.0	0	0	0	1-60
17	40	M	66	Fr. tibia	2.15	++	++	++	++	+		++	++	++	full pupillary dilatation and extreme dryness
				Fr. tibia											

N, normal medical student; 0, no change; ++, maximum change (i. e., increase in heart rate of 30 to 40 beats per minute; full pupillary dilatation and extreme dryness of the mouth). All mental changes consisted of slight dizziness.

N, normal medical student; 0, no change; ++, maximum change (i. e., increase in heart rate of 30 to 40 beats per minute; full pupillary dilatation and extreme dryness of the mouth). All mental changes consisted of slight dizziness.

In the first few experiments small doses of novatrine were given but it soon became evident that they had neither toxic nor cumulative effects and subsequently very large doses were exhibited. This cautious attitude explains, in part at least, the failure to obtain a true toxic point in the early subjects.

Seven individuals were made toxic (in the sense already defined) with novatrine, in doses ranging from 68 to 273 mg. and averaging 143 mg. The minimal toxic dose of atropine for these same persons ranged from 2.15 to 3.25 mg., with an average of 2.54 mg. The corresponding

ratio of minimal toxic doses of atropine and novatrine ranged between 1:32 and 1:84, with an average ratio of toxicity of 1:54. In this connection, it is noteworthy that not only were fewer subjects intoxicated with novatrine but that, with 2 exceptions, these reactions were quantitatively less severe than the reactions experienced after atropine.

**Conclusions.** 1. The average ratio of minimal toxic dose of atropine and novatrine was 1:54.

2. No cumulative effect was observed after daily administration of large doses of novatrine.

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## CONCENTRATED AQUEOUS HEPARIN

## A NEW FORM OF INTRAMUSCULAR ADMINISTRATION

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THE importance of intravascular thrombosis and its attendant morbidity and mortality now is generally realized. Interference with the coagulation of blood by the administration of an appropriate drug is a feasible and logical approach to the problem of intravascular thrombosis. Of the substances employed for this purpose heparin most nearly approaches the ideal. Its intravenous administration, even in interrupted form, is attended by too many difficulties to permit of general use. Loewe and his collaborators<sup>1</sup> have reported the use by the subcutaneous route of heparin in Pitkin's menstruum. Dicumarol is also commonly employed, having the advantage of oral administration. The necessity for frequent prothrombin determinations during its administration, the occasional occurrence of serious bleeding from overaction of the drug and the inability to arrest this excessive action promptly limit its use. Neither heparin in its present forms of administration nor dicumarol meets the requirement of an anticoagulant which can be administered simply, safely, painlessly and accurately for the general prophylaxis and therapy of venous thrombosis.

This communication describes the clinical utilization of a new preparation of concentrated aqueous heparin which can be administered intramuscularly. It has proved valuable in inhibiting coagulation in thrombophlebitis, phlebothrombosis, postoperatively as prophylactic therapy against venous thrombosis and as an adjuvant to the use of dicumarol in various thrombotic states. The total num-

ber of cases (115) treated has been small and inadequate for statistical analysis but the technique of the use of the drug has been so simple and the justification for its widespread use so apparent that our experiences should be recorded at this time.

Studies with the intramuscular administration of heparin in the dilute solution (10 mg. per cc.) commercially available, led us to the use of a concentration of 100 mg. in 1 cc. Such a solution of concentrated aqueous heparin,\* free from foreign substances or the vasoconstrictor agents and watery in appearance and viscosity, has been administered intramuscularly under our supervision for about a year. The medication was usually injected by nurses into the gluteal muscles with the regular intramuscular syringes and needles at 8 to 12 hour intervals. Individual doses of heparin have varied from 50 to 180 mg., the smallest doses being given to patients weighing 90 pounds or less and the largest to those over 180 pounds. Our data are not complete enough at the present time to permit the formulation of exact schedules of administration, for patients vary in their heparin requirement. We have not attempted to ascertain the reasons for this except to observe a rough correlation with the body weight. Adequate prolongation of the coagulation time of the blood is usually attained in patients weighing between 100 or 130 pounds by administering 100 mg. every 8 hours or 120 to 140 mg. every 12 hours. In heavier individuals larger doses may be required. The maximum

\* Prepared and supplied by the Lederle Laboratories, Pearl River, New York, through the kindness of Dr. Stanton M. Hardy.

daily dose should not exceed 450 mg. The successful heparinization in patients weighing over 170 pounds may be obtained by giving 1 mg. of heparin per pound of body weight as the initial dose and between 0.5 and 0.7 mg. of heparin per pound at 8 hour intervals subsequently.

The medication was administered over a period of several months to most of the postoperative patients of a general surgical service, including a considerable number of thoracic cases and sympathectomies for hypertension. The cases were not selected; the ages varied from 17 to 70 years (though the majority of the patients

bed and walking. There was no existing intravascular thrombosis in this group of 90 patients and none developed venous thrombosis. Bleeding at the site of operation was observed several days after the inception of the heparin regimen in 3 cases early in the series. It was found that this complication could be averted if the anticoagulant were withheld until 48 to 60 hours had elapsed after operation. In a second group of 25 patients, most of whom had recently experienced thrombophlebitis or coronary artery thrombosis, bleeding was not observed. Hemorrhage into an internal organ was never observed.

TABLE 1.—THE EFFECT OF A SINGLE INTRAMUSCULAR INJECTION OF CONCENTRATED AQUEOUS HEPARIN ON THE COAGULATION TIME OF 18 DIFFERENT PATIENTS

Weight of patient (lbs.)	Heparin (intramus.) (mg.)	Coagulation time* (peak)	Coagulation time† (last test)	Time of last test‡
110 . . . . .	100	3	-2	1½
118 . . . . .	150	8	6	2½
121 . . . . .	175	0	-5	1½
210 . . . . .	200	35	0	20
150 . . . . .	200	88	-2	20
150 . . . . .	200	80	6	20
110 . . . . .	160	40	40	5½
120 . . . . .	175	78	78	5½
149 . . . . .	150	20	10	12
108 . . . . .	150	35	35	8
129 . . . . .	150	28	28	8
118 . . . . .	150	65	35	8
150 . . . . .	150	35	20	12
151 . . . . .	150	12	12	8
156 . . . . .	150	12	12	8
180 . . . . .	180	29	20	8
122 . . . . .	120	15	10	8
168 . . . . .	170	10	10	8

\* The number of minutes above the control coagulation time at the peak of the effect of heparin.

† The number of minutes above (or below) the control coagulation time when the last test was performed.

‡ The number of hours after the injection of heparin that the last test (previous column) was performed.

were over 40 years) and both sexes were included. Many of the patients were febrile because of their disease and received other medication such as vitamins, blood transfusions, sulfonamides or penicillin. Since a considerable number of cases of carcinoma are included, the nutritional and metabolic status of not a few of the patients was poor. Almost all were in bed. The administration of heparin was usually started 24 to 72 hours after operation and was continued for a variable period or until the patients were out of

One of the practical advantages of this method of heparin administration was the ease with which the anticoagulant effects could be controlled. In our first trials the coagulation times (Lee and White method) were performed at frequent intervals in order to insure an adequate but not extreme anticoagulant effect. At the present time 1 coagulation determination daily, immediately before the administration of a dose, is found to be adequate. If the result of this test reveals complete cessation of heparin effect, a dose some-

what larger than the previous one is given. If, on the other hand, a satisfactory prolongation of the coagulation time (18 to 24 minutes) is observed, the dosage is not changed. If the coagulation time is found to be over 24 minutes, either a smaller dose is ordered or the injection is postponed for 2 hours. Coagulation tests done at other intervals after injections reveal prolongation beginning  $\frac{1}{2}$  to 1 hour after the initial injection. The greatest prolongation is observed 4 to 6 hours after

needles. In only rare instances did a hematoma appear at the site of injection and this was never large. A reaction which occurred in 2% of the injections consisted of a palpable and occasionally tender nodule up to 3 cm. in greatest dimension. Frequently the patients were not aware of these nodules which were absorbed despite continuation of the drug. In a small number of instances included in the above, nodules were not palpable but patients complained of some pain at the site of

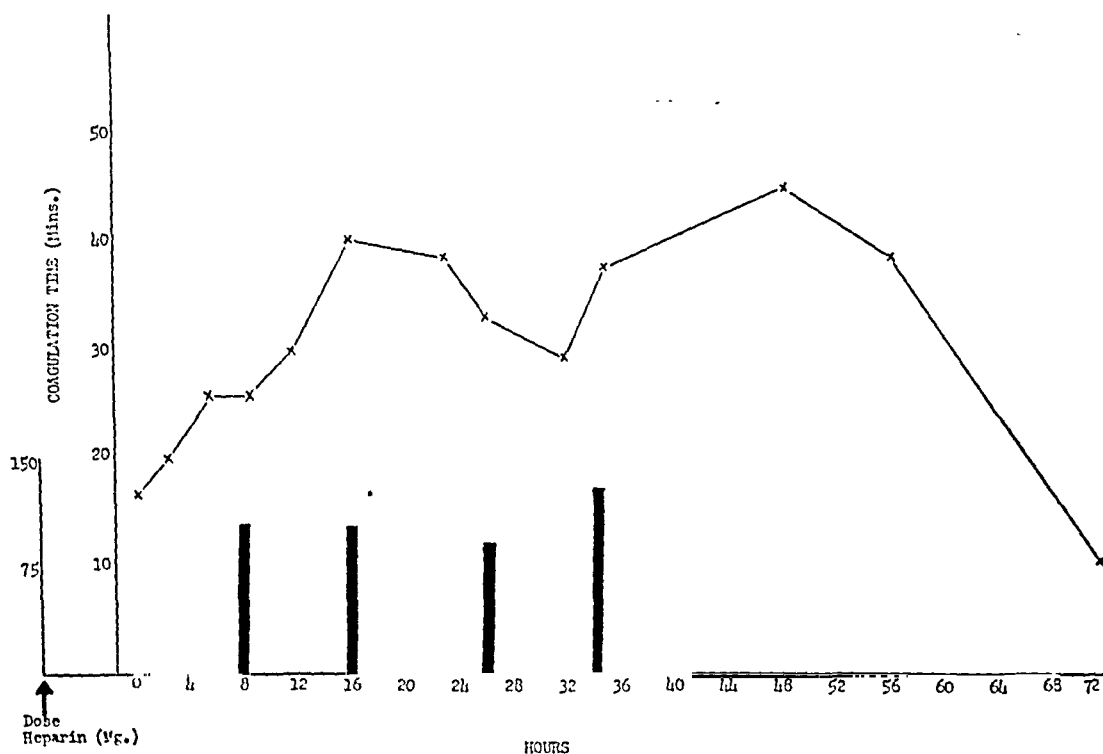


CHART 1.—The effect of repeated intramuscular injections of concentrated aqueous heparin on the coagulation time.

an injection, and, with the doses of heparin which we administer, varies between 25 and 60 minutes. Prothrombin or other determinations are not required. The table and chart which follow illustrate some of the effects mentioned.

As previously noted, the injections were given with the usual syringes and needles, specifically 20 gauge,  $1\frac{1}{2}$  inch needles. This technique was followed in order to maintain the customary ward routine. Since the heparin is in an aqueous medium, it can be given easily with 22 or 24 gauge

injection. This was never severe enough to require analgesics. With the use of finer needles, the incidence of local reactions probably could be reduced.

In the small series of cases of thrombophlebitis that we have treated, we have observed the same rapid subsidence of fever, tenderness and edema in the affected extremity that others have described with different preparations of heparin or other anticoagulants. Some of these patients were treated for periods as long as 3 weeks.

We have taken advantage of the prompt



action of heparin in administering it to 10 patients who were concurrently treated with dicumarol. Approximately 48 hours after the commencement of the conjoint therapy, the heparin was discontinued when the prothrombinopenic effect of dicumarol was evident.

The authors wish to express their gratitude to Dr. Myron Steinberg for assistance with part of this work.

**Summary.** Concentrated aqueous heparin (100 mg. per cc.) is a new, simple, safe and essentially painless form in which the drug can be administered intramuscularly in order to achieve a desired anticoagulant effect.

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## DEGENERATIVE BONE DISEASE

## FINDINGS IN 18 CASES WITH POSTERIOR SPURS OF THE LUMBAR VERTEBRÆ

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THE presence of spurs or osteophytes on the posterior aspects of the bodies of the lumbar vertebræ has not received much consideration. Therefore it seems desirable to describe 18 cases. In reviewing the literature relatively few references are listed. Two recent articles in the foreign literature<sup>13,14</sup> describe sciatica produced by thickening of the posterior margins of the lumbar vertebræ or by posterior spondylarthrosis. Bailey and Casamajor<sup>1</sup> in 1911 report 1 case of spinal "osteoarthritis" in which a posterior spur was considered to be the cause for compression of the spinal roots in the lumbar area, and Parker and Adson<sup>8</sup> in 1925 reported 5 patients in whom bony spurs of the lumbar spine were thought to be the cause of low back pain and definite neurologic changes. In the latter report the Roentgen examination revealed only lateral exostoses but at operation "an overgrowth of soft, spongy, vascular bone producing a marked narrowing of the spinal canal was found." Larmon<sup>6</sup> in a study of 10 unselected spines obtained at autopsy found that "posterior lipping of the fifth lumbar vertebræ occurred in 4 specimens. In each case the osteophyte formation was located in the foramina and produced narrowing of the anterior diameter. All cases were associated with moderate to severe degenerative changes in the disk substance. Compression of the nerve root was evident in 2 of the spines." Although most writers do not mention the presence of such spurs, Shore<sup>9</sup> makes a definite statement after the examination of 106 spines from an anatomic museum and osteophytes never occur on the posterior portion of the bodies of the vertebræ.

In the cervical region the presence of spurs projecting posteriorly has received

considerable attention during the past few years. The spurs may involve several cervical vertebræ or may be limited to only one. These osteophytes may encroach upon the nerve canal causing various symptoms and lead to serious neurologic changes which may partly be due to the anatomical arrangement of the cervical spine in which the roots emerge from the dura mater at right angles and also the factor that the intervertebral foramina decrease in size from the upper to the lower cervical vertebræ whereas the corresponding spinal nerves actually increase in size.<sup>3</sup> Hadley<sup>4</sup> has shown from cadaver specimens how the foramina in the cervical region may be reduced to one-fourth normal size by bony or fibrous tissue encroachment and nerves "crowded into the lower portion of the opening or become flattened in a ribbon-like manner or even completely destroyed." Several investigators<sup>5,7</sup> believe the condition follows damage to the intervertebral disk at the site of the bony spur rather than pressure of the spur itself on the root. Spurling and Scoville<sup>10</sup> state that "in many instances the herniated portion of the disk is surrounded by bone and that these bony prominences may project into the intervertebral foramina."

The incidence of posterior spurs in the lumbar area as observed in the writer's experience is shown by the following figures. In the 7 months covered by this report, 7251 patients were admitted to an Army general hospital in New Guinea. During this time the Roentgen ray department examined 910 spines; of these, 629 involved the lumbo-sacral region. Eighteen cases (approximately 3%) of the lumbo-sacral examinations showed spurs arising from the posterior surfaces of the

bodies of the vertebræ. To compare the incidence of this lesion with that of the usual arthritic conditions of the spine: a diagnosis of osteoarthritis was made in 168 cases with the familiar hypertrophic changes of lipping on the anterior or lateral aspects of the vertebræ. Fifteen cases of ankylosing spondylitis or rheumatoid arthritis of the spine were found. During a preceding 22 months period the same hospital organization functioned in Australia. During this time the total hospital admissions numbered 33,000 and a total of 2800 examinations of the spine were made. However, only 1 case of a posterior spur was reported while in Australia. The incidence of osteoarthritis and rheumatoid arthritis of the spine was relatively the same during the 2 periods.

Analysis of the 18 cases in this series reveals that the average age was 33 years ranging between 21 and 39 years. Two-thirds of the patients recalled an acute injury to their backs which required bed rest or cessation from their civilian work for a varying period. The time between the initial injury and the admission to the Army hospital varied from 3 months to 25 years with the average approximately 6 years. Many of these patients did have symptoms after entering the Army; however, only 2 were unable to complete the strenuous basic training of a soldier. All the men were sent overseas, and it was not until they suffered a second injury or their discomfort became severe did they finally enter the hospital.

The symptoms in the lower back on admission varied from mild discomfort to severe disabling pain. In 2 patients the complaints were typical of osteoarthritis, that is, they were of a dull aching nature aggravated with changes of position and of the weather, whereas in the other 16 patients the symptoms were similar to the herniated disk syndrome with pain worse at night and on coughing or sneezing, with a history of partial or complete remissions between attacks and with radiation of pain down the posterior part of the leg to the foot or down the lateral

or medial aspects of the thigh. The examination of 12 patients showed the loss of diminution of the normal lumbar curve, spasm and tenderness of the lumbar muscles, limitation of motion in the lumbar area and a positive straight leg raising sign. The Achilles tendon reflex was absent in 3 patients and paresthesia of the leg was found in 1 patient.

The laboratory findings included: a complete blood count which was normal in all cases; the blood test for syphilis was also negative in all cases; the sedimentation rate was elevated in only 1 patient in whom a diagnosis of rheumatoid arthritis of the spine was also made. Lumbar punctures were done on all the patients. The spinal fluid determinations of globulin, gold curve and Kahn were normal in all patients. The total protein of the spinal fluid of the 18 cases ranged between 16 to 48 mg. with the average for the group of 30 mg.

The Roentgen rays in the straight lateral view demonstrated the presence of these spurs on the inferior aspects of the bodies of the vertebræ. They were found on the second lumbar vertebra in 1 case, on the third lumbar vertebra in 3 cases, on the fourth lumbar vertebra in 4 cases and on the fifth lumbar vertebra in 10 cases. The size of the spurs measured from 2 to 6 mm. in length. A spinogram with oxygen was done on 1 patient. The air column showed a slight impression upon the anterior subarachnoid air column which was the sight of the bony spur. A filling defect at a lower level was also found. This patient had minimal objective signs.

None of these patients was subjected to operation while overseas. Several were returned to the United States for further observation and treatment while others were returned to duty, and thus no further information is available.

The clinical history and findings of 2 illustrative cases are as follows:

**Case Reports.** CASE 1. Patient P.R. was a 21 year old white male who in civilian life

injured his back while diving 2 years before admission to the hospital. He had difficulty during his basic training and was placed on light duty. The pain in his back was constant, worse at night and aggravated by changes in the weather. There was no radiation of the pain. The examination disclosed a loss of the lumbar curve, tenderness on pressure of the lumbar vertebræ, the lumbar muscles were tender and spastic, the motion of the back was limited in all directions due to pain and the straight leg raising sign was positive on the right. No other abnormal neurologic findings were found. The laboratory work was normal. The Roentgen ray (Fig. 1) showed a large bony spur with

aggravated by coughing and standing. He was transferred to the general hospital after the acute symptoms had subsided at which time the physical examination revealed only tenderness on palpation of the lumbar vertebræ. The motion of the back was normal and no neurologic changes were found. The Roentgen ray (Fig. 2) showed a posterior spur on the body of L-3 with considerable lipping on the anterior margins of all the lumbar vertebræ.

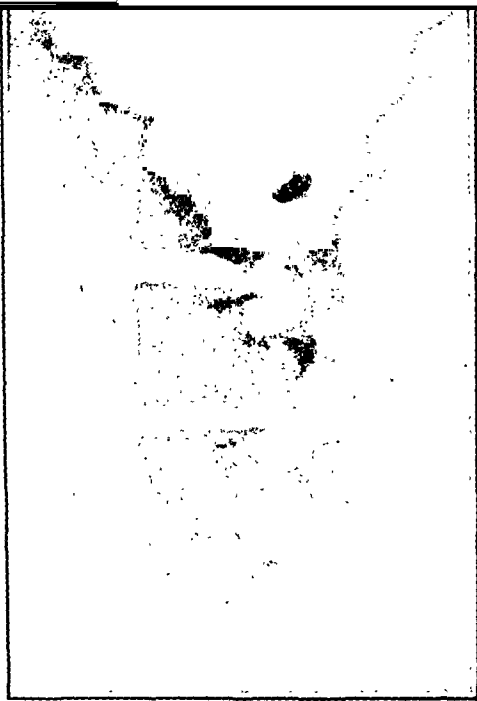


FIG. 1.—Posterior spur on inferior aspect of body of fourth lumbar vertebra.

almost complete bridging on the posterior inferior aspects of the body of the fourth lumbar vertebra.

**CASE 2.** A 37 year old soldier, 3 years before admission, suffered an injury to his back which kept him in bed for 3 weeks. He had no difficulty in his strenuous army life until 1 month before entering the hospital, when on attempting to crawl out of a trench, he was taken with acute pain in his back so that he had to be carried to the hospital. The pain was constant and was

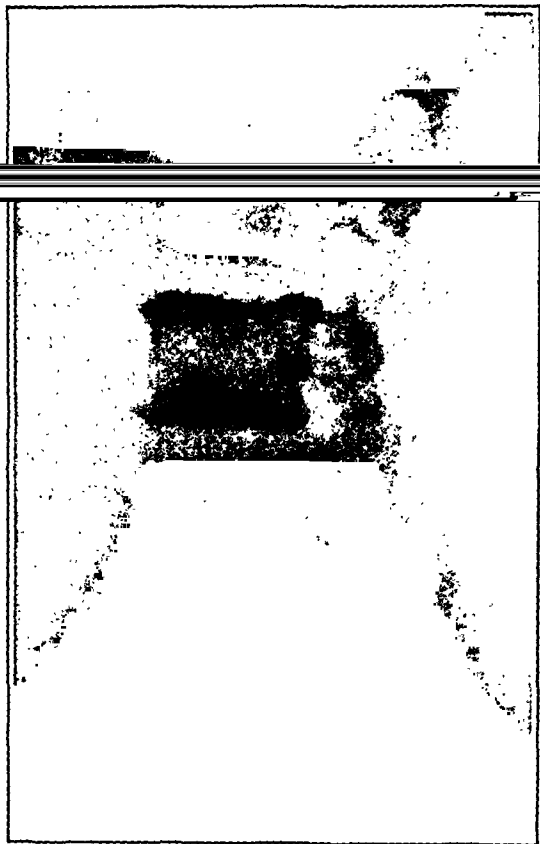


FIG. 2.—Posterior spur on posterior aspect of the body of third lumbar vertebra and spurs on anterior aspects of other vertebræ.

**Discussion.** Why do the spurs develop in these particular areas? Many investigators believe that degenerative changes in the spine are the result of lesions in the intervertebral disks. The idea is proposed that either complete or partial rupture of the nucleus pulposus may occur with subsequent degeneration and evidence of proliferation of the margins of the bodies of the vertebræ. Keyes and Compere<sup>5</sup> in their study of the intervertebral disk show that with damage to the disk, the weight

of the body is transferred to the lateral and anterior portion of the vertebra leading to sclerosis and lipping of the spine. They injured the disk posteriorly in dogs and allowed the nucleus pulposus to exude and found in a period of 3 months at the site of the injury "a marked hyperostosis and new bone formation very similar to that observed clinically in cases of marked osteoarthritis of the spine." In the cervical area Stockey<sup>11</sup> noted the secondary calcification of the nucleus pulposus due to herniation. Stress and strain or improper mechanics have been considered by Bennett and Bauer<sup>2</sup> who found that by displacement of the patella in rabbits they were able to produce marked lipping of the femur in a period of 4 weeks. The occurrence of exostoses at the margin of the vertebræ in scoliosis also lends support to this idea. Changes in blood supply have been suggested as a possible etiologic factor and there are those who favor an infectious process, a form of local infection in the joint or area. Weems<sup>12</sup> considers an inflammatory process as the cause of calcification of disks in children since in childhood these structures have a

blood supply so that infections elsewhere can be carried to them by the blood stream.

The interpretation of the symptoms and clinical findings depend upon the position of the spurs and any change they may undergo. These osteophytes may have been present before the latest attack, and it was not until some pathologic change, as yet unknown, in the local area made their presence manifest.

This study is presented to call attention to the presence of these spurs in the lumbar area which are apparently more frequent than is usually considered. This report may encourage further observations and lead to additional speculation as to etiology.

**Summary.** 1. A survey of 629 spine examinations made in patients with low back pain showed posterior spurs of the bodies of the lumbar vertebræ in 18 cases.

2. Signs of root irritation were found in 12 cases.

3. Due to the exigencies of military service, these patients could not be followed sufficiently to prove the relationship of spurs to symptoms.

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## THE RÔLE OF PULMONARY VESSELS IN THE REFLEX CONTROL OF THE BLOOD CIRCULATION\*

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RESEARCH done during the last decades has substantially enlarged our knowledge of the reflex control of the blood circulation. This research has particularly demonstrated the great importance of the neuroreflex influences which arise in the cardiovascular system itself. To the number of such thoroughly investigated reflexes which regulate blood circulation and are connected with the activity of the pressoreceptors of the vascular bed of the systemic circulation, belong: the depressor (cardio-aortic) reflex, the carotid sinuses reflexes, and the superior and inferior vena cava reflexes.

Thanks to these data, the hypothesis about reflex "self-regulation of the blood circulation" has, at present, a firm foundation through an immense factual material. However, all these scientific data are not perfect because we are still lacking the knowledge of the inner mechanics and interrelations of the known reflexes, and also because we are still without a full knowledge of all reflexes regulating the blood circulation. Particularly the pressoreceptor rôle of the vessels of the lesser blood circulation has been quite insufficiently investigated. For this reason we decided to devote our research to this problem.

Experimental research previous to ours on the pressoreceptor function of pulmonary vessels was conducted by 3 workers only: Schwegk<sup>14</sup> (1935), Schweitzer<sup>13</sup> (1936), and de Burgh Daly and co-workers<sup>2</sup> in 1937. Of these studies, only the work of Schwegk gave more or less clear indications that the reflex influence of increased blood pressure in pulmonary vessels changes the rhythm of the heart

rate and the condition of the blood-vessels of the systemic circulation.

However, the literature on this subject has many data which indicate indirectly the possibility of reflexes from pulmonary vessels. In this class belong first of all the experimental and clinical observations on the pulmonary embolism which show that not only are the mechanical factors important but also equally so the neuroreflex factors which play a great rôle especially at the initial stage of the embolism.

Although almost all authors agree that the priority in this question belongs to the German scientists, Schumacher and John<sup>12</sup> (1914), our extensive study of the literature on the subject convinces us that the honor of this discovery belongs without any doubt to 2 Russian scientists, A. Fokht and B. Lindeman.<sup>5</sup> In 1908 these men demonstrated that after the section of the pulmonary branches of the vagus nerve an embolism produces less disturbance of the cardiovascular activity. They emphasized the function of reflex factors in the whole symptom-complex of an embolism of a pulmonary artery.

A series of clinical observations of the pulmonary embolism forced many others, such as Sauerbruch,<sup>10</sup> Edens,<sup>4</sup> Frey,<sup>6</sup> Binger and Moore,<sup>1</sup> to come to the same conclusions.

The experiments of Scherf and Schönbrenner<sup>11</sup> in 1937 raised the question of a possibility of reflexes from pulmonary vessels on the basis of a similarity between electrocardiograms of an embolism of a pulmonary artery and of a myocardial infarct due to a thrombosis of the ramus descendens of the left coronary artery. As, at the autopsies of 2 patients who had

\* A lecture given at a special meeting of the Philadelphia Physiological Society and the Philadelphia Chapter of the American-Soviet Medical Society.

the above-mentioned symptoms during their illness, these authors did not find any organic changes in the myocardium or coronary vessels, they concluded that the essence of the lesion lies in a spasm of coronary vessels produced by the reflex action from the pulmonary vessels.

However, subsequent observations of many authors did not support the existence of such a "pulmo-coronary" reflex.

Morphologic data also lead us to believe that reflexes from pulmonary vessels may exist. Thus, long ago, in 1898, a Russian histologist, Dogel,<sup>3</sup> described numerous nerve endings of sensory type in the walls of the pulmonary artery. Analogous findings have been reported by many authors up to the present day.

Taking into consideration the absence in the literature of exact information upon the reflexogenic rôle of pulmonary vessels, we decided to pursue these facts further.

As to the choice of experimental methods, we followed principally the basic methods of Schwiegk.

**Methods.** For the experiments we used cats weighing 2 to 3 kg. Under chloroform and other anesthesia, we cannulated the right common artery and vena saphena magna. At the same time we performed tracheotomy and intubated the trachea. After that, through a cannula in the vena saphena, we injected a 10% solution of urethane. Following this, the entire experiment was conducted under urethane anesthesia. Having induced an artificial respiration, we opened wide the left half of the chest and cannulated the left pulmonary artery and ligated the pulmonary veins of the same side. As a result, the left lung kept its innervation intact, but was completely isolated from the main blood circulation. The gas exchange evidently was performed only by the right lung. The cannula in the left pulmonary artery was connected with rubber tubes filled with Bayliss 8% gum acacia Ringer solution and also connected with a mercury manometer and with a simple device which allowed changing of the pressure in pulmonary vessels.

In all experiments a mercury or membrane manometer was used for registration of the pressure in the right common carotid artery.

In some series of experiments, electrocardiographic registration was taken, also venous pressure and pressure in one of the branches of the pulmonary artery of the right lung, which was not separated from the main blood circulation; also in some series of experiments changes of the volume of the spleen were taken, etc. Briefly, we made 103 experiments of this kind.

**Results.** In all our experiments in which the operation was accomplished without complications and the animal was in good condition, increase in pressure in pulmonary vessels which had been separated from the general blood circulation always induced a fall of blood pressure in the arteries of the greater circulation, and also in most instances, the pulse rate was diminished. This fall of pressure in the arteries of the greater circulation was clearly indicated even at comparatively small increases of pressure in the pulmonary vessels (see Figs. 1 and 2).

The fall of arterial pressure of the greater circulation showed a definite ratio with the increase of pressure in the pulmonary vessels. Figures 1 and 2 indicate the character of this ratio. The fall of the pressure starts after a latent period of about 2 to 3 seconds. With repeatedly increased pressures in pulmonary vessels, the reaction showed a tendency to a gradual diminution, which could be attributed to the development of a pulmonary edema.

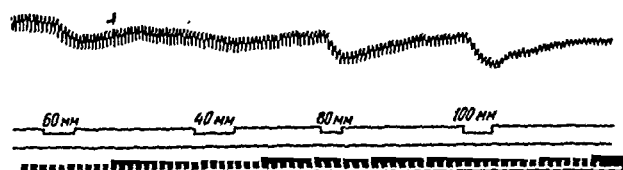
The reflex character of the phenomenon is fully confirmed by the results of experiments in which the section of the left vagus nerve on the neck was accomplished. Thus, Figure 3*A* showed a common reaction. Figure 3*B* demonstrates a curve which has been registered during the same experiment, but after the section of the left vagus nerve. There is no change of pressure in the right common carotid artery, despite the increase of pressure in pulmonary vessels up to the very high level of 100 and even 130 mm. of mercury.

If we analyze the reactions due to increase of pressure in the pulmonary vessels, we come to the conclusion that these reactions, as a rule, are results of the change

in frequency of heart beat (heart component) and also the change in vasomotor reaction of vessels of the greater circulation (vasomotor component). In some experiments these components manifest them-

selves quite independently. However, in the majority of cases, the reaction is a result of simultaneous changes from the heart and from the blood-vessels.

The changes in pulse rate are usually



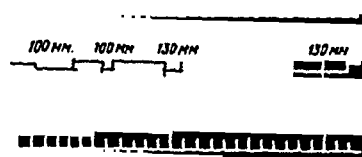
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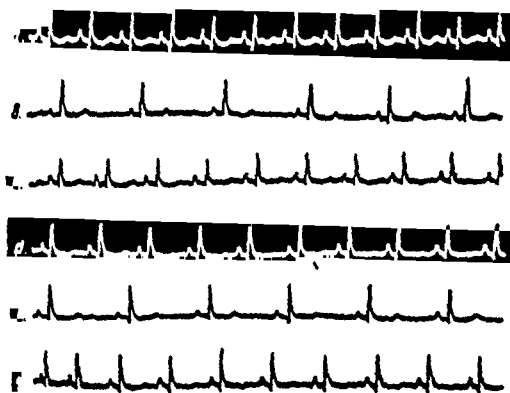
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3 A



3 B



4



5

FIG. 1.—Fluctuation in the carotid pressure produced by distention of the left lung at pressures as indicated. Cat. Time record at 10 second intervals. (4/9/39.)

FIG. 2.—Experiment of the same type as Figure 1. (5/7/39.)

FIG. 3A.—Responses as before with intact vagus. (5/9/39.)

FIG. 3B.—Repetition of the experiment after section of the vagus.

FIG. 4.—Effects of lung distention on the pulse rate as indicated by the electrocardiograph. (a) Control; (b) 80 mm. pressure in pulmonary vessels; (c) 40 seconds and (d) 80 seconds after release of pressure; (e) repeated distention of pulmonary vessels; (f) return to normal. (12/2/39.)

FIG. 5.—Reaction to distention showing a marked after-effect. (12/1/39.)



very pronounced and consist on the average of a diminution of the rhythm from 25 to 30% in comparison with the starting level. In a few cases, we see a diminution of the rhythm of more than half. For a more detailed analysis of the reaction of the heart we performed many experiments with electrocardiographic registration of the heart activity. These experiments convinced us that the changes of the heart activity are expressed only in the slowing down of the rhythm without any great changes of the form of the curve, or conduction time, etc. A typical example of these experiments is given in Figure 4. The results of these experiments are quite contrary to the above-mentioned results of Scherf and Schönbrunner, who claim the existence of the pulmocoronary reflex.

We believe that our findings show without any doubt that the electrocardiographic changes of myocardial infarct type in cases of the embolism of the pulmonary artery are due only to mechanical disturbances of blood circulation and gas exchange, and express only different degrees of oxygen lack of the myocardium, and do not present any reflex influences.

Coming to the analysis of the vasomotor component, we will first describe the reaction of the arterial part of the vascular tree. The absolute depth of the fall of the arterial pressure showed individual variations. Taking the average, in the majority of cases, the increase in the pressure of the pulmonary vessels of 40 to 50 mm. of mercury induced the fall of the pressure in the arteries of the greater circulation of 20 to 30 mm. At a higher starting level of arterial pressure, its fall as the result of a reflex from pulmonary vessels was more sharply marked. The fall in pressure occurred, as a rule, without variations, reaching the peak 25 to 40 seconds after beginning of the stimulation. In a few instances, however, the fall in pressure occurred so rapidly, that the curve showed a great similarity to the classic curve which results from stimula-

tion of the peripheral end of the vagus nerve.

In the majority of cases, the curve of blood pressure showed considerable after-effects, reaching up to 20 to 40 seconds and in some cases even more. An example of this is Figure 5. As to the mechanism of the vasomotor response, we believe that in our case the fall of the arterial pressure is the result of the pronounced dilatation of the arterioles in different parts of the systemic circulation entirely similar to that produced by depressor or carotid sinus reflexes. In support of this fall of the vasomotor tonus we too found a considerable increase in the amplitude of the pulse pressure at the time of the reflex response.

To elucidate the changes occurring in veins, we made a series of experiments and registered the venous pressure (jugular vein, by means of a water manometer). The results were absolutely similar: in all cases we registered an increase in venous pressure. This is illustrated in Figures 6 and 7. The character of these changes is quite evident and does not need comment.

We did not obtain identical results in our experiments when trying to register the blood pressure in a branch of an artery of the other lung, which was not excluded from the blood circulation.

We observed in the opposite pulmonary artery pressure changes which were not large and at the same time not consistent in the direction of the response. Still, we must remember that the question of participation of pulmonary vessels in depressor and carotid reflexes is still not absolutely settled and is undergoing further investigation.

Inasmuch as the spleen is regarded as a "blood depot" and plays an active rôle in many vasomotor reactions of the organism, we decided to study this organ in connection with these reflexes, especially as the spleen is so easily accessible for experiment.

In these experiments with oncographic registration of the volume of the spleen, we found that this volume increases in

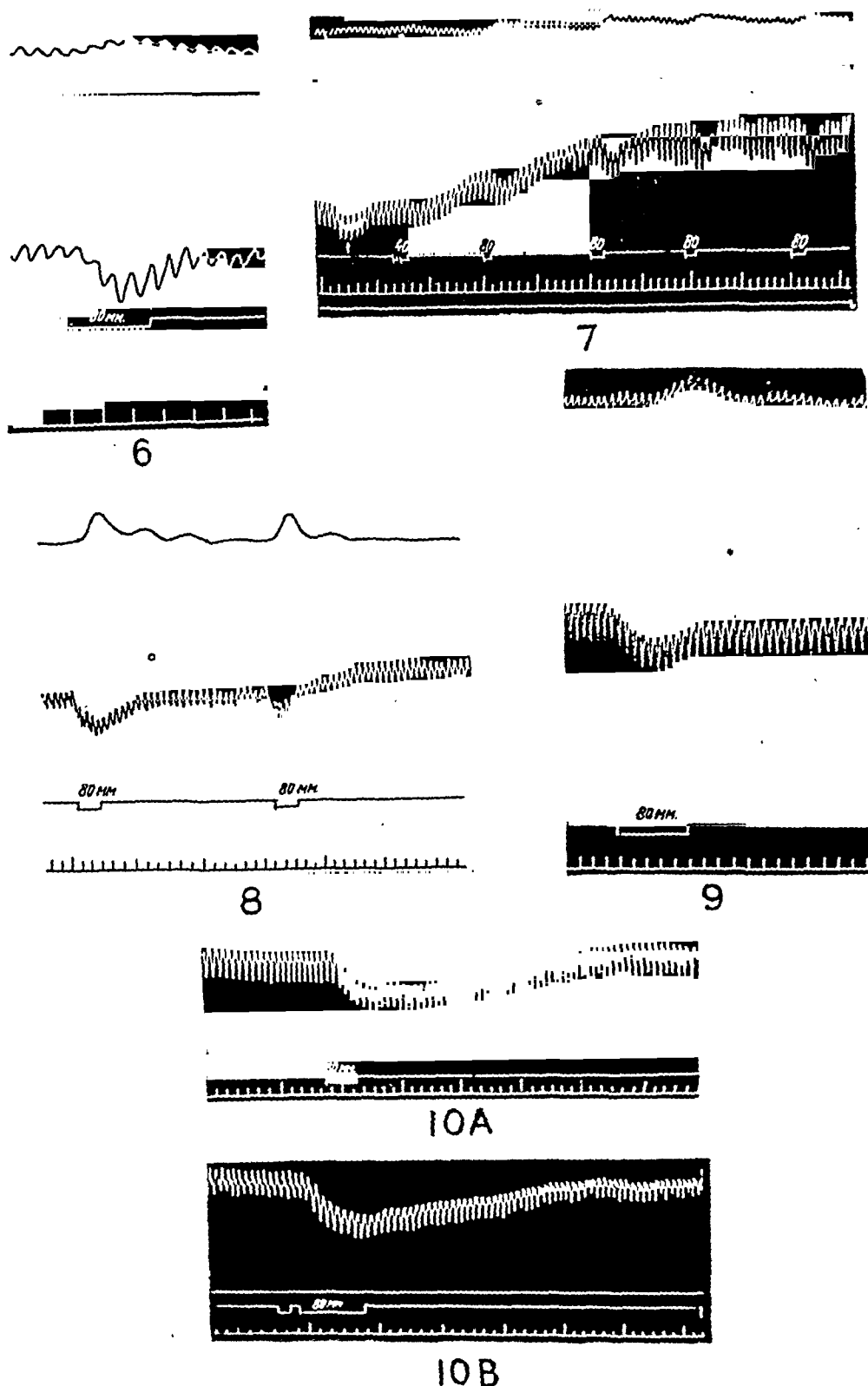


FIG. 6.—1, Record (top) of pressure in the right jugular; 2, base line of jugular pressure; 3, arterial pressure; 4, signal; 5, base line of arterial pressure; 6, time 10 second intervals. (11/3/39.)

FIG. 7.—Observations as in Figure 6. (11/17/39.)

FIG. 8.—Record of splenic contraction and blood pressure as a result of the distention of the left lung. Time in 10 second intervals. The splenic record is shown above and the arterial pressure below (6/7/39.)

FIG. 9.—Record of the same type as Figure 8. (6/9/39.)

FIGS. 10A and 10B.—Record 10A was obtained with a distention of the pulmonary vessel and 10B was obtained later after the denervation of carotid sinuses in the same animal. (11/22/39.)

proportion to the increase in the blood pressure in the pulmonary vessels. This reaction (increase of volume) evidently shows the active participation of the spleen in the general fall of the systemic arterial blood pressure, reflexly elicited at the increase of pressure in pulmonary vessels (see Figs. 8 and 9). The active part the spleen plays in these experiments could be demonstrated when the spleen nerves were cut. In such cases we saw complete lack of any reaction of the spleen when the spleen was denervated.

We also tried to investigate the interrelation of this reflex with those from the carotid sinuses. In the study of the functional interrelations between separate pressoreceptor zones of the greater circulation, 2 kinds of facts are recognized.

It was found that, by simultaneous stimulation of both depressor or both sinus nerves, the fall of pressure is greater than by the stimulation of only one of them. There exists, therefore, a definite physiologic summation.

These interrelations present, in our opinion, a real physiologic interconnection between the 4 pressoreceptor nerves of the arterial part of the greater circulation, because in natural conditions the pressure changes during a given period of time simultaneously in the whole beginning part of the arterial stream.

The receptors which are situated in the aorta and the carotid sinuses are, thus, simultaneously subjected to equal stimulations by intravascular pressure and send equal impulses to the centers which control the blood circulation.

We think that it is quite different with the second series of facts on the basis of which conclusions about a definite antagonism between pressoreceptor nerves are made. In the conditions of an experiment, such an antagonism, a definite counteraction of the intact pressoreceptor zones to the change of the pressure caused by the stimulation of the central end of one cut pressoreceptor nerve, is sufficiently established. Hering,<sup>7</sup> for instance, found that in case of preservation of the normal

innervation of one carotid sinus, the stimulation of the central end of the other sinus nerve gives a smaller effect than after cutting of the sinus nerves on both sides. Hering found the same also in respect to the depressor nerves. The same interrelations are found between carotid sinuses and depressor nerves in similar conditions of experiments.

The essence of this antagonism consists in that (due to the tonic character of the stimulation of the pressoreceptors which occurs reflexly under the influence of the isolated artificial stimulation of one of them), the fall of blood pressure lowers the intensity of inhibitory impulses from other pressoreceptors which preserved the normal connection with the vascular stream.

As a result, we find an opposite picture, the pressoreceptors become no longer brakes, "a bridle," as picturesquely described by Hering, but stimulators, "a whip," the pressure shows a tendency to an increase, thus counteracting a complete expression of the effect of an artificial stimulation.

We believe that this antagonism has no real physiologic importance and exists only in the specific artificial conditions of an experiment which radically distorts the normal interrelations between conditions prevailing in separate receptor zones. We have already emphasized that in actually physiologic conditions the pressure in the region of all pressoreceptors of the arterial part of the greater circulation can, in a certain period of time, change only in the same way, so that the receptors of the aorta and of the carotid sinuses are in regard to the intravascular pressure always under similar conditions.

In our experiments, the increase of this pressure occurred in a vascular region which was excluded from the general blood circulation. The conditions of our experiments could, therefore, to a certain degree be compared with an isolated stimulation of one separated sinus or depressor nerve while the other receptor zones were intact, or can be compared with an increase of pressure inside of a sinus isolated from the

blood circulation (*e. g.*, according to the "*cul de sac*" method of Moissejeff.<sup>9</sup>)

In order to elucidate this question, we made a series of experiments with an increase of pressure in pulmonary vessels before and after a denervation of the carotid sinuses.

In all experiments, we recorded the reaction of the blood pressure on an increase of the pressure in the pulmonary vessels at first with normal innervation of the carotid sinuses. Then we denervated both sinuses, and after a while we repeated the experiment after the denervation.

As a result of our experiments, we saw in the majority of cases relations similar to those which, as previously described, are seen in analogous conditions between carotid and depressor reflexes.

An example of such an increase of the effect after denervation of carotid sinuses is seen in Figure 10B. In this experiment, the increase of the pressure in pulmonary vessels to 80 mm. Hg caused a fall of pressure in the carotid artery to 40 mm.

At the same time, a considerable prolongation of the period of the after-effect is to be seen; 4 minutes after the first stimulation and  $3\frac{1}{2}$  minutes after the second, the pressure had not returned as yet to the starting level (before denervation of the carotid sinuses, the period of after-effect in this particular experiment is also quite considerable; however, 2 minutes and 40 seconds later, the pressure had already reached the previous level).

In some experiments we did not notice any remarkable increase of the reaction after denervation of carotid sinuses, in the sense of a greater depth of the fall of pressure. We observed, however, almost always a marked prolongation of the period of after-effect.

If we take into consideration that during our experiments we almost always observed a tendency to a gradual weakening of the strength of the reaction and to a shortening of the period of after-action in the course of an experiment, then the changes just mentioned obviously

clearly express the change of the reaction after denervation of the carotid sinuses.

To sum up, we think that we are entitled to the conclusion, based on the series of experiments, that in case of a functional exclusion of the carotid sinuses, the reflex from the pulmonary vessels is characterized by a greater intensity.

We believe that we can prove that an increase of pressure in the vessels of a lung which has been excluded from the general blood circulation, causes extensive changes of the whole circulatory system which have incontestably a reflex character.

These changes consist in a reaction of the heart (slowing down of the rhythm) as well in vascular changes (extensive dilatation of the vessels). The basic character of the hemodynamic change in the investigated reflex is accordingly analogous to the reactions observed in depressor and carotid reflexes, though it is not so strong as the latter. Therefore, the reflex from pulmonary vessels should, together with the depressor and carotid reflexes, have an appropriate place among the reflex mechanisms which play an important rôle in the "automatic" regulation of the blood circulation.

From the general point of view, the investigated reflex should be classed as to type and number with the so-called moderator-reflexes ("*Entlastungsreflexe*" of Hess<sup>8</sup>) of the cardiovascular system. In the greater circulation, similar reflexes originate as a result of a stimulation by the increased pressure of the pressoreceptors which are situated in the beginning part of the arterial stream (aorta, carotid sinuses).

The physiologic meaning of these reflexes consists in securing of changes which return an increased pressure to a more or less normal level which would not cause an overload of the heart.

From this point of view, the depressor reaction at an increased pressure in the vessels of the lesser circulation is fully analogous to the reaction which can be

observed at increased pressure just in the arterial part of the greater circulation.

On the basis of such considerations, one can theoretically assume that the present reflex originates in the arterial stream of the small circulation.

De Burgh Daly assumed that the reflex, which interests us, originates in the sensory endings in pulmonary veins, but we think it strange to assume, from the point of view of the physiologic significance of proprioceptive reflexes of the cardiovascular system, the presence of a reflex of a depressor type at an increase of pressure in the venous part of the vascular stream. Actually, the increase of the venous pressure manifests itself usually as a result of a functional deficiency of the heart and a further weakening of the heart activity in these conditions (depressor reaction) would be unable to restore the blood circulation to a normal level. It would on the contrary increase the degree of deficiency and result in causing a peculiar vicious circle.

In analogy to reflex regulation in the greater circulation, it is known that the increase of pressure in the vena cava causes not a depressor reaction but a pressor one, increase in frequency of the heart action and a slight increase of arterial pressure (Bainbridge reflex, 1920). As a result of the increase of the heart action, the filling of the venous part of the vascular stream is diminished and thus this reflex plays a substantial rôle in the regulation of the whole blood circulation. In our opinion, the same should be expected in regard to the pulmonary veins and we regard the venous part of

the pulmonary vascular tree also as a possible source of origin of reflexes not of depressor but of a pressor nature.

We think it necessary to clear this question by a new series of experiments with a perfusion of pulmonary vessels, *i. e.*, in conditions near to the normal in the meaning of interrelation of pressure between arterial and venous parts of the pulmonary vascular stream.

In regard to the functional significance of the reflex from pulmonary arteries, we have already mentioned that the character of the obtained reactions shows that it undoubtedly represents a typical moderator reflex. The specific situation of receptor zones of this reflex in the arterial part of the pulmonary circulation reflects its predominant rôle in preventing an overload of the right heart.

In such increases of pressure in the arterial part of the pulmonary vascular stream as they may arise in a number of physiologic and pathologic conditions (Valsalva's experiment, embolism of the pulmonary artery, and others), the reflex from pulmonary arteries, by lowering of the heart action and by causing a transfer of the blood into the greater circulation *via* an extensive vasodilatation and an increase of the capacity of the depôt, prevents the weak musculature of the right ventricle from being overburdened by work. At the same time, this reflex has probably some significance in the prevention of a pulmonary edema which, as is well known, easily occurs in a case of a prolonged increase of pressure in the system of the pulmonary artery.

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OBSERVATIONS ON THE VELOCITY OF THE BLOOD IN NORMAL MEN  
IN THE BASAL STATE\*†‡

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MEASUREMENT of the velocity of the blood by determining elapsed time between injection of material intravenously at one site and evidence of its appearance at another is in wide popular use as a diagnostic measure. In a recent study of convalescence<sup>5</sup> we tested blood velocity with the material described by Spier, Wright and Saylor<sup>6</sup> commercially available as Macasol.¶ Kvale and Allen<sup>1-4</sup> have worked with this same material, reporting normal standards much like those found by Spier, Wright and Saylor. Discrepancies between our findings and those above mentioned led us to reexamine the standards for this test and assess its variability in our own hands. We find a normal range of blood velocity significantly greater than previous workers and a significant difference in the average blood velocity as well. Our findings indicate that measurement of the blood velocity is not as useful as many believe because the relatively wide range of "normal" values overlap the "abnormal" values in the very cases where the differential significance of the test would be most important.

*Material and Methods.* Of 46 normal men, each was in the basal state, that is, had not eaten since the evening meal the night before and either remained in bed until the test was done or returned to bed for an hour after reaching the laboratory. Of these men, 34

were military personnel who had completed the reconditioning program at Thayer General Hospital which included a 10 mile hike under full pack; 12 were civilians who had been hospitalized some months before but who had returned to usual health, were engaged in their ordinary activities and showed no clinical evidence of disease. The mean age of the men tested was 25.6 years; the extremes were 18 to 40 years.

Instructions were given to the subject in a stereotyped way with reassurance that nothing untoward would happen. The subjects were supine. The arm with the largest antecubital vein was drawn a little away from the body and supported at about the level of the auricle. The vein was entered cleanly with an 18 gauge needle and the tourniquet released several minutes before the test. Two ml. of Macasol were injected as rapidly as possible. The stop watch was started at the beginning of the injection. The observer reported times to a recording assistant as the patient announced end points at the tongue, the hands, the perineum and the feet. After subsidence of all sensation from the first test, a second test was carried out through the same needle. No attempt was made to distinguish between time to the right and left hand or to the right and left foot.

The mean of the 2 tests was entered as the circulation time for that individual. In the statistical analysis standard deviations were based upon these means and the number of individuals tested. This differs from the

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† Thayer General Hospital patients were studied through the cooperation of Brigadier General Henry C. Pillsbury, Officer Commanding, Lt. Col. Richard Stetson, Chief of the Medical Service, Major Donald Ferguson, Chief of the Reconditioning Service and other members of the staff.

‡ This work was done in the Lung Station of the Department of Medicine, a laboratory organized under a grant from the Commonwealth Fund, and some of the equipment used was available through a grant by the Ciba Pharmaceutical Products, Inc.

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¶ Supplied through the courtesy of the Nepera Chemical Company, Yonkers, New York.

analysis employed by previous authors<sup>1,6</sup> in that they derived standard deviations from the total number of tests done rather than the number of individuals tested.

Close scrutiny of our data revealed a systematic difference between 2 observers. In 16 cases tested by Observer A the mean arm to tongue circulation time was 18.1

TABLE 1.—CIRCULATION TIME IN SECONDS TESTED WITH MACASOL

"Normal subjects" of both sexes reported by other authors compared with "normal men" in the basal state reported in this paper.

Subjects	Circulation time in seconds, arm to:			
	Tongue	Perineum	Hands	Feet
Spier, Wright and Saylor: <sup>2</sup>				
35 normal subjects, 40 tests:				
"Resting"—mean	14.6	21.5	26.2*	27.9*
average deviation	$\pm 3.23$	$\pm 4.59$	$\pm 5.26$	$\pm 7.1$
range	7-22	12-32	11-43	10-48
Kvale and Allen: <sup>3</sup>				
13 normal subjects, 73 tests:				
"Basal"—mean	13.8	21.2	23.6*	34.1*
standard deviation	$\pm 2.65$	$\pm 5.14$	$\pm 5.74$	$\pm 9.65$
range—class	5-24	10-34	10-39	15-59
51 normal subjects, 102 tests:				
"Resting"—mean	13.7	21.0	23.5*	32.1*
standard deviation	$\pm 3.52$	$\pm 5.52$	$\pm 6.04$	$\pm 9.59$
range—class	5-29	10-44	10-44	20-69
Men reported in this paper:				
46 normal men, 92 tests:				
"Basal"—mean	16.7	26.0	28.1	37.4
standard deviation	$\pm 4.8$	$\pm 8.4$	$\pm 6.6$	$\pm 9.5$
range	9-30	13.5-56	18.5-48	23-63

\* Average of right and left hand or right and left foot.

TABLE 2.—EFFECT OF ANXIETY ON BLOOD VELOCITY

Successive reconditioned soldiers tested in an open ward. Coefficient of correlation between time of injection and observed arm to tongue time is  $0.66 \pm 0.28$ .

Elapsed time from entry on ward (min.)	Arm to tongue time (seconds)	
	Observer A	Observer B
8	14	10
16	17	9
24	15	13
32	Blank	14
40	22	14
48	21	11
56	20	18
64	30	No test
Mean	19.8	12.7

RESULTS. Our data are presented in Table 1 together with the results of Spier, Wright and Saylor<sup>6</sup> and of Kvale and Allen.<sup>1</sup> The arm to tongue time was  $16.7 \pm 4.8$  seconds, the arm to perineum time was  $26 \pm 8.4$  seconds, the arm to hand time was  $28.1 \pm 6.6$  seconds and the arm to foot time was  $37.4 \pm 9.5$  seconds.

seconds whereas an entirely comparable group (tested actually on the same days and in the same place) showed a mean of 13.4 seconds and the difference was statistically significant. Part of this difference was found due to the habit of 1 observer to read the watch to the mark ahead of the moving hand while the other read to the mark behind in tests conducted with a pendulum appearing from behind a partition. While this difference could amount only to a second, recalculation of the data corrected for this no longer showed a significant difference between observers.

On 1 occasion evidence of anxiety influencing the test was apparent. In a ward of Thayer General Hospital 15 soldiers were distributed 7 along one wall and 8 along the opposite. Explanation of the test had been given the night before and all were under supervision through the night. Tests were made early in the morning before the men had risen. Preparations were made in an adjoining room. Two teams entered quietly and moved



down the ward. Tension was obvious in the men first tested, while the later subjects relaxed as they saw no ill befall their predecessors. As the teams moved down the ward, there was a progressive increase in the circulation time observed. We estimated the time of each injection from the start of the experiment. These elapsed times are tabulated with the corresponding arm to tongue time in Table 2. It is apparent at once that there is a correlation between the time elapsing from the start of the test and the observed blood velocity. The coefficient of correlation is highly significant statistically.

Correlations were attempted between circulation time and the height, weight, age and pulse rate of those subjects where these data were available and none was found. The variation in all of these measures was small, however, due to the nature of the subject material. No seasonal difference was observed between 2 groups studied, 1 in mid-summer, the other in early winter.

**Discussion.** The results reported by Spier, Wright and Saylor<sup>5</sup> give only "average deviation" while Kvale and Allen<sup>1</sup> based their "standard deviation" upon the total number of tests rather than upon the number of individuals, so, exact statistical comparison is impossible. It is evident that our mean times are longer in all categories than are those of the other observers. In the case of the arm to tongue time our mean of 16.7 seconds is 2.1 and 2.9 seconds longer respectively than that of Spier, Wright and Saylor and that of Kvale and Allen.

We followed the analysis we used because it has been shown<sup>1</sup> that variation of blood velocity is greater from individual to individual than upon repeated testing in the same individual. Since practical interest centers in comparing an individual to a "normal standard" it appears wise to broaden the biological base in the statistical analysis. Thus, if one enters the calculation of the standard deviation with the best estimate of circulation time available for the individual, which is the aver-

age of duplicate or multiple determinations, one minimizes the consistency of results in the same individual and emphasizes the variation between individuals. For this reason, pooling of all values irrespective of the individuals from whom they arise seems to us an erroneous approach because it takes no true account of the number of individuals tested; that is, the real size of the biological sample.

Our data on convalescent patients reported elsewhere<sup>5</sup> illustrate the error into which one might have been led by accepting the narrow "range of normal" previously reported. Convincing evidence that our convalescent patients were indeed within the normal range was obtained when follow-up studies upon return of these patients to normal health revealed a mean change of only  $-0.4$  second in arm to tongue circulation time; i. e., no change at all.

It seems unusual that there was no difference between blood velocity in basal subjects and blood velocity in subjects who had merely rested for a few minutes as found by Kvale and Allen.<sup>1</sup> We have no data on this point but there were only 13 subjects in their "basal" group and perhaps a larger sample might have revealed a higher mean. Another point concerns sex differences where again we have no data. The observations of others have not been broken down to show sex difference.

When the standard deviation is calculated in a manner to give due weight to biological variation it is seen that a considerable latitude must be allowed for "normal" circulation time. The extremes of our observed range were 9 to 30 seconds for arm to tongue time. The  $\pm 1$  standard deviation is considered to include approximately 68% of cases and  $\pm 2$  standard deviation which is commonly considered a more reliable "range" includes 95% of cases. From our data these ranges would be from 11.9 to 21.5 seconds, or 7.1 to 26.3 seconds respectively. If the clinician chooses the smaller range he must resign himself to error 1 time in 3.

No untoward reactions of any kind occurred. Two of our 46 subjects experienced no end-point reaction. One patient, not a member of this normal series, seemed to "pool" the material in his arm because, while no end-point sensation occurred at first, later, as he moved his arm to arise, he experienced the spreading sensation characteristic of this agent. Kvale and Allen<sup>1</sup> have discussed fully other factors in "blanks," a term used to designate failure of the subject to perceive a sensation of warmth in the area.

The evidence of the effect of anxiety is interesting. One may question whether a patient exhibiting anxiety is "basal" and obviously he is not in the academic sense of the word. However, in practical use of any physiological test, experience has shown that anxiety is frequently encountered and contributes to the variability in results whether in normal subjects or patients who are ill.

**Summary and Conclusions.** 1. Duplicate determinations of the blood velocity of 46 normal male subjects in the basal state were made with the calcium-magnesium salt mixture of Spier, Wright and Saylor<sup>6</sup> (Macasol).

2. The arm to tongue time was  $16.7 \pm 4.8$  seconds, the arm to perineum time was

$26 \pm 8.4$  seconds, the arm to hand time was  $28.1 \pm 6.6$  seconds and the arm to foot time was  $37.4 \pm 9.5$  seconds.

3. These times are significantly longer than those reported by Spier, Wright and Saylor<sup>6</sup> and by Kvale and Allen.<sup>1</sup> This discrepancy is discussed.

4. The normal variation of blood velocity is greater than commonly recognized. This variation impairs the accuracy of this test as a diagnostic measure among the patients in whom otherwise it would be most useful.

5. Systematic differences occurred between the data of the 2 observers and a reason was found to account for this discrepancy.

6. In addition to many previously reported factors affecting the determination of blood velocity, anxiety as a factor could be evaluated in one of our experiments.

7. There was no simple relation between the velocity of the blood and the height, weight, age or pulse rate of these normal young men nor was any seasonal variation perceptible.

8. No untoward reactions of any kind occurred and end-points were secured in all but 2 subjects.

9. One additional reason for "blanks" is described.

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## FURTHER CONSIDERATION OF THE QT INTERVAL

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PART I. INTRODUCTION. So much has been written about the measurement of systole, both mechanical and electrical, that any further comment must reasonably be accompanied by new information. Three types of information will be presented: (1) a description of the "bundle of His" as it appears in the human fetal heart; (2) measurements of QT duration in various species; (3) data acquired in acute experiments designed to modify the QT interval. In addition, deductions regarding cardiac diagnosis as well as the deductions concerning intraventricular conduction will be made.

The terms "mechanical systole," "electrical systole" and "Q-T" as they appear in the literature should be defined. Any 1 of the 3 terms indicates a measurement of ventricular contraction. When measurements are made by the use of mechanical devices such as suspension levers, cardiac plethysmographs, delicate levers (or mirrors) attached to the heart, pressure manometers of various types, or by the recording of heart sounds, the term "mechanical systole" is employed. The measurements obtained are conditioned not only by the physiologic state of the heart being investigated but by the specific characteristics and mechanical limitations of each different recording device. When the electrocardiograph came into general use the term "electrical systole" appeared. This period was measured from the beginning of the Q wave to the end of the T wave and was supposed to include the time required for 4 processes, namely: the passage of the action current over the bundle of His, and over the ventricular muscle; the actual ventricular contrac-

tion; and the recovery. Electrocardiographic explanations have changed with the years; Burch and Windsor<sup>6</sup> now write:

"The Q-T interval represents the time required for depolarization and repolarization of the ventricular musculature. This interval coincides *closely* with ventricular systole, as systole begins, essentially, with the peak of the R wave and ends with the termination of the T wave. The interval is measured from the beginning of the QRS complex to the end of the T wave (see Chapter I). It varies considerably with age, sex, and cardiac rate. When the rate is rapid the interval is short and when it is slow the interval is long."

"The Q-T interval *varies inversely with the calcium level of the blood*. In hypoparathyroidism, uremia, after vomiting or forced breathing, if the calcium blood level is low, the interval is prolonged. In hyperparathyroidism if the blood calcium level is high, the interval is shortened. Digitalis shortens the interval. Toxic states, myocardial ischemia, and many types of cardiac disease, such as rheumatic, diphtheritic, arteriosclerotic, and hypertensive, prolong the interval. A prolonged Q-T interval frequently indicates the presence of myocardial intoxication. This may or may not be reversible."

Scattered quotations from the paper by Blair, Wedd and Young<sup>5</sup> add further viewpoints:

"In the intact heart, Q-T duration covers that time from the depolarization of the first activated area to the time of repolarization of the last area to recover. The well-known dependence of Q-T on heart rate is due not only to the cumulative effects of rate, but to each diastolic interval as it occurs. It is suggested that after exercise

\* Student Research Fellow of the Life Insurance Medical Research Fund.

the Q-T interval may be a more sensitive index of the *state of the muscle* than is heart rate. It cannot be denied that there is a third factor determined by the heart rate which simultaneously arrests contraction and starts repolarization. It is very probable that the relation of the Q-T interval to the duration of the beat will ordinarily hold for the whole heart."

A starting point for analysis is offered by one further sentence contained in the summary of the article by Blair, Wedd and Young,<sup>5</sup> namely: "Evidence is presented that repolarization arrests the contractile process in the muscle leading to the conclusion that the electrical processes control the mechanical rather than the mechanical the electrical."

This phrase deserves emphasis. Ashman and Hull also regard the electrical change as primary: "Under normal conditions, therefore, the electrical change apparently induces the mechanical, that is, the local flow of action current in each segment of muscle initiates the contractile response in the same segment" (p. 16).<sup>2</sup> Thus, if mechanical and electrical recording were equally perfect one would expect contraction time and QT to be identical in a single cell. Also considering the entire heart, contraction in no part can begin before Q nor can contraction in any part outlast the end of T, provided the electrodes are optimally placed and sensitivity is adequate to record all that actually occurs. It is possible that recorded mechanical systole may be shorter than electrical systole (time required to develop tension, instrumental lag, etc.), but because contraction ends with repolarization mechanical systole cannot outlast electrical under the conditions specified. Hence any conclusions based on the measurements of mechanical systole which are longer than electrical systole must be rejected.<sup>13</sup> If mechanically recorded data agree with adequately recorded electrical data then conclusions based on measurements of "mechanical systole" may be used to corroborate those based on electrical measurements. How-

ever, if mechanical and electrical measurements do not agree, the latter must be accepted.

The clinician and the biophysicist seem in sharp disagreement when White and Mudd<sup>29</sup> write: "The measurement of the duration of the Q-T of the electrocardiogram is apparently of little or no clinical value," but Blair, Wedd and Young<sup>5</sup> state: "It is suggested that after exercise the Q-T interval may be a more sensitive index of the state of the muscle than is heart rate."

PART II. HISTOLOGIC STUDIES AND THEIR IMPLICATIONS. Critical reviews of the connections of the conducting system in various species can be found in the literature and need not be recapitulated here.<sup>8,17,27,30</sup> More recently it has been questioned whether the human heart (and that of the dog) really possess a conducting system composed of specialized tissue.<sup>11</sup> Nonidez<sup>19</sup> reports one present in dogs and monkeys and describes the parasympathetic nerve supply to this tissue.

Serial sections of 3 human fetal hearts were available in this laboratory for study; they were stained by Masson or Mallory techniques. One was supplied by the Carnegie Institute of Washington, courtesy of Dr. George Corner, and the others were prepared by Dr. Cornelius T. Kaylor of this University. In each of these human hearts, tissue which stains unlike ventricular heart muscle, and which has a connective tissue sheath can be identified.<sup>21</sup> When this tissue is reconstructed from the serial sections it is found to have a distribution similar to that commonly called the "bundle of His" and its branches and peripheral expansions as seen in ungulates. From the main bundle and from the chief branches of the bundle, multitudinous fibers emerge which can be followed, but only for short distances, until they imperceptibly change into cells having the same staining reaction and appearance as cardiac ventricular muscle (see Figs. 1, 2 and 3). All histologists have noted this imperceptible change which is invariably an axial (end to end) transition. These



FIG. 1.—A frontal section through the septum of the heart, showing above the membranous septum (collagen staining blue). The 3 upper arrows indicate the capsule (staining blue) of the bundle of His (staining mauve). The lower arrow indicates the left bundle branch streaming downward subendocardially. Note the numerous connections to septal muscle. (Mag.  $\times 55$ .)

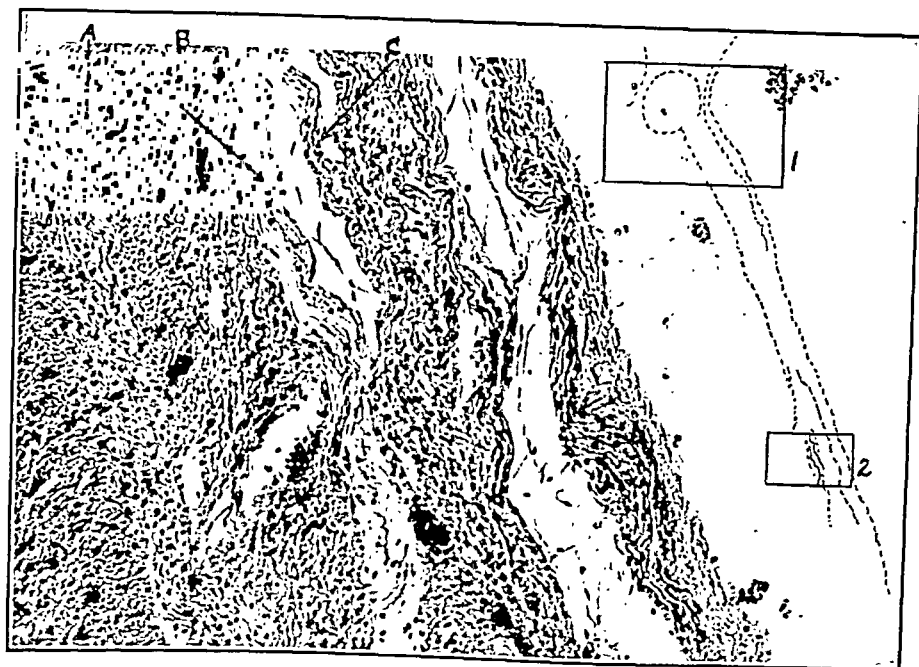


FIG. 2.—Detail of left ventricular margin of the septum. The photomicrograph shows 3 conducting system strands (see arrows A, B, C). Note that the tip of arrow C lies near the transition from the large clear-celled conducting fiber above to the narrower, less clear, more deeply stained muscle cell below. (Mag.  $\times 215$ .) The pen sketch indicates the locale of Figures 1 and 2 on a different scale.

connections are numerous and strands continuously leave the main bundles, so that numerous small islands of muscle are supplied by successive offshoots.\*

**Discussion of Part II.** Do what we have supposed to be physiologic facts agree with such an anatomic arrangement?

several syncytia, why is it that so many physiologists have reported that there is no spread of current for any great distance along a single band on the surface of the heart?<sup>212</sup>

If small islands are successively activated, one must inquire: (a) Has syncytial



FIG. 3.—Heart of a 580 mm. long beef embryo. Terminal twigs of the conducting system enlarged 230:1. See S.54 a Purkinje fiber with 5 terminal transitions into heart muscle. (Wahlin, Figure 24.)

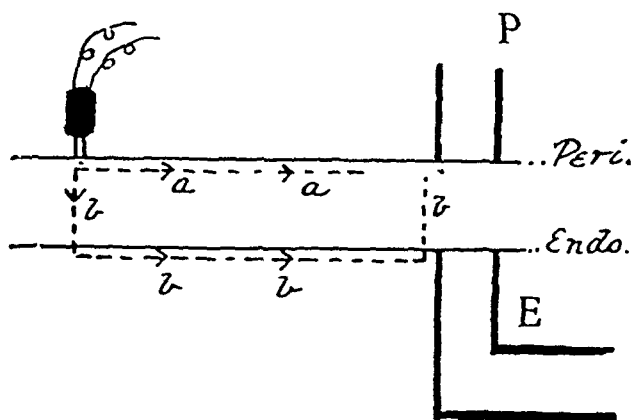


FIG. 4.—A diagram showing alternative paths (a-a, b-b) which an artificially induced excitation wave may take in the heart wall. (Lewis, Mechanism and Graphic Registration of the Heart Beat; courtesy of Hoeber, Inc.)

It has been said that the ventricular muscle is a syncytium, 1 huge interconnected mass of muscle. If this be so, first of all how could so many anatomists<sup>22</sup> be convinced that the mammalian ventricle is made up of several distinct muscle bands? Even if the concession were made, that the ventricles contain not merely 1 but

spread over long surface areas been proven or disproven, (b) Is there evidence in the literature which would support this theory, and (c) What prevents generalized spread? Most writers have not found evidence of surface spread over long areas (consult Harris<sup>12</sup> for Bibliography). Reports of at last 3 investigators could be interpreted

\* See also Truex, R. C., and Copenhaver, W. M., *Am. J. Anat.* 80, 173, 1947.

to support the theory that limited areas of tissue are activated.

An experiment described by Lewis<sup>14</sup> (on page 92) is pertinent (see Fig. 4). Let us assume that when the path *b-b* was followed the stimulating electrodes were sufficiently separated from the epicardial contact to be on different "islands." Then, conduction had to be retrograde *via* a muscle cell and thence by a conducting path to a junction and then forward again to a second island. But note the sentence: "*If the stimulating electrodes are nearer to the contacts, the wave may reach P along the path a-a.*" Here is experimental proof that "syncytial" spread along the surface layer of the heart is very limited. This experiment does not necessarily prove that conduction is *faster* in the Purkinje tissue than in heart muscle, it does prove that from one point on the heart's surface an impulse can be driven in a retrograde manner and that eventually another surface area is activated. It does prove that an artificial stimulus did not spread across the surface syncytium when the stimulating and the recording electrodes were well separated (20 to 30 mm.). The conduction rate of heart muscle (on the surface) would need to be measured from 2 contacts sufficiently near to be on the same "unit." This experiment of Lewis suggests that such units are of macroscopic dimensions. The main difference between this experiment of Lewis and those of Robb and Robb<sup>23</sup> was the "nearness" of the 2 electrodes. The latter showed that if the electrodes were sufficiently near and a cut were made between them, the intrinsic wave failed to reach the distal electrode. Robb's hypothesis of conduction along a muscle bundle would need to be restated with this modification that there is not "syncytial" spread of depolarization along even 1 muscle bundle for any very great distance but that the "conducting" system is so arranged that successive areas along a given muscle bundle are depolarized sequentially. Moe, Harris and Wiggers<sup>18</sup> when analyzing the initiation of fibrilla-

tion write that their experiments failed to show that the fibrillating process necessarily spreads in the direction of surface bundles and specifically state: "Such observations disprove the possibility that development of fibrillation is contingent on passage of repeated long reërrant waves over both ventricles by common fasciculi of fibers." However, Ashman and Hull<sup>2</sup> (page 48) write: "It is not unlikely that in the ventricles, as in the auricles, the impulses are conducted more rapidly lengthwise through muscle bundles than transversely. Yet the syncytial character of the muscle would seem to assure transverse as well as longitudinal conduction."

Because of the histologic arrangement described above, if a wave of depolarization sweeps from conducting tissue to heart muscle cells this movement has to be parallel to muscle fiber direction. Furthermore, in order to be recorded, the passage of current must be axial, because if a wave of depolarization started in the center of a cell (arriving on a non-existent pathway) and spread in opposite directions, these currents would neutralize and no potential would be recorded. Failure of stimuli to spread from one region to another is doubtless related to the refractory phase because if a wave of depolarization reaches adjacent areas *almost* simultaneously these areas would be resting and refractory at *almost* identical times also.

Quoting from Ashman and Hull (page 70):<sup>2</sup> "Alfredson and Sykes point out that in spite of the much larger heart with thicker walls in cattle, the QRS interval averages only 0.09 second against 0.08 for man. *This is further evidence that the intramural branches of the Purkinje net work are relatively poorly developed in man.*" This conclusion is not the only possibility; one is equally justified in concluding that the conduction system is so efficiently arranged in each species that the whole mass of the beef heart is activated about as quickly as is the whole mass of a human heart, and each of these is

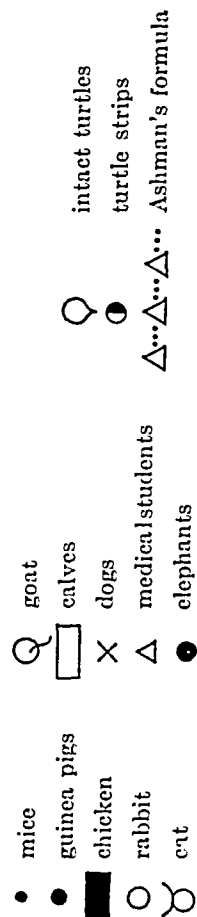
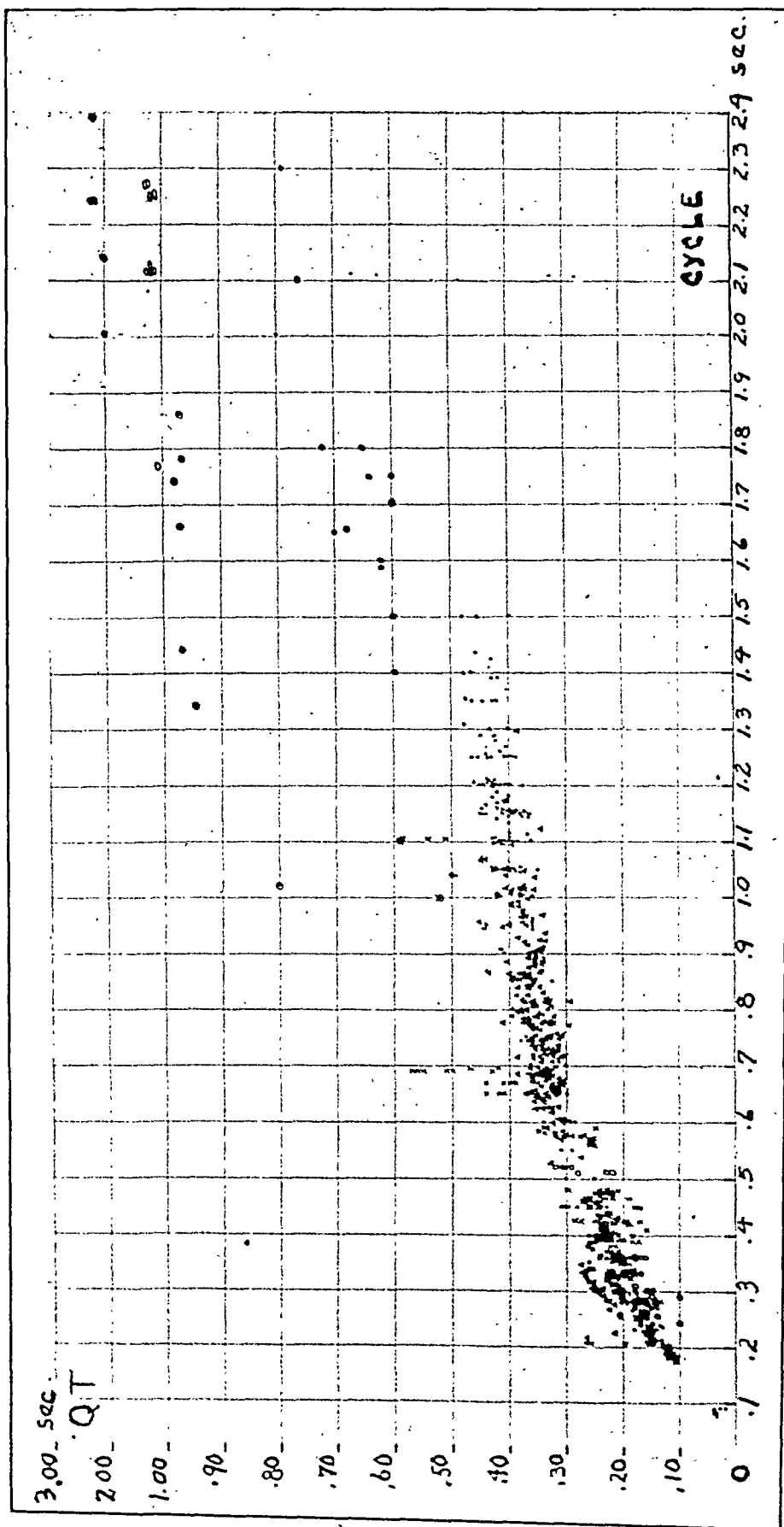


FIG. 5.—A scatter graph showing QT and cycle values:



activated about as quickly as a turtle heart, or a turtle heart strip.

PART III. MEASUREMENTS OF QT TO CYCLE RATIO IN VARIOUS SPECIES. When QT and cycle duration in seconds are plotted on coördinate paper, a definite relationship appears (Fig. 5). Also QT and cycle values in seconds for mice,<sup>20</sup> guinea pigs, rabbits, cats, babies,<sup>7</sup> puppies,

of these many factors might have altered the accuracy of the figures reported. It seems truly remarkable that in spite of all the possible errors there is such a degree of constancy, for with little spread, a straight line relationship appears. The slope of this straight line is not the same as that found by Schlamowitz.<sup>28</sup> The reason may be that he included extremes

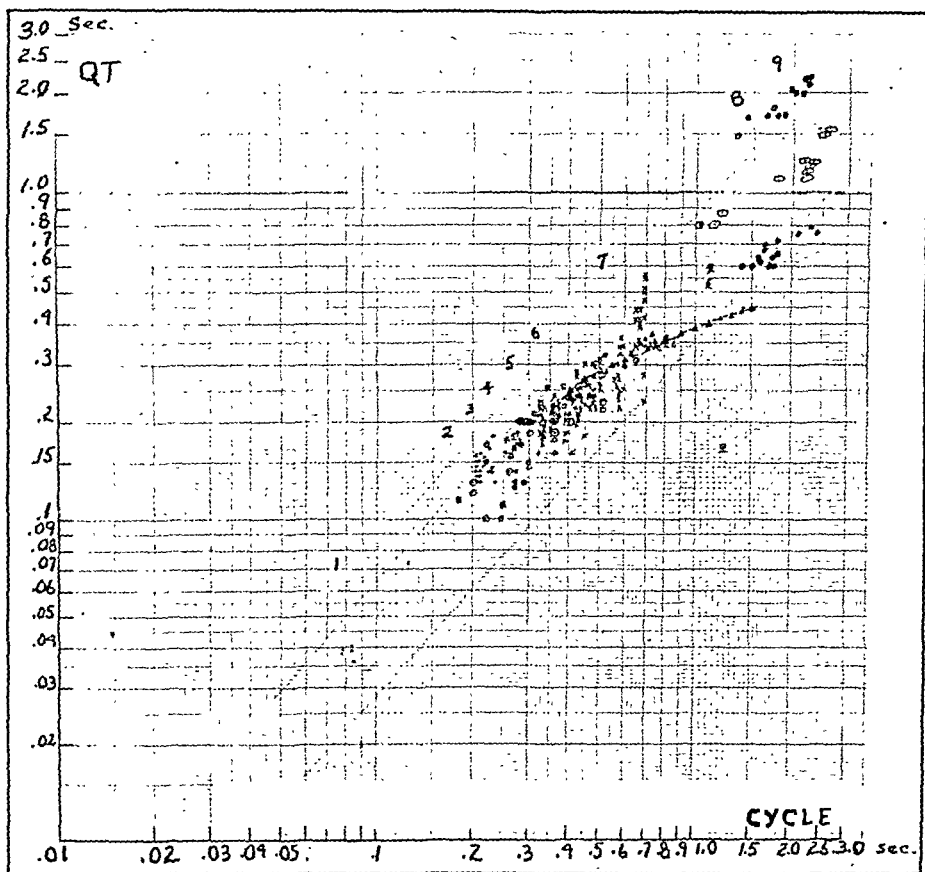


FIG. 6.—A scatter graph plotted on double logarithmic paper showing QT and cycle values for various species; symbols as in Figure 5

medical students, dogs, calves, a goat, elephants,<sup>28</sup> turtles, and turtle heart strips<sup>5</sup> were plotted on double logarithmic paper (Fig. 6). The unanimity of the result is the more surprising since the data were obtained under divers conditions by many workers,<sup>1,5,7,23,29</sup> using various types of recording apparatus and with paper running at varied speeds. Any one or several

of cycle duration far outside the "normal" range for man.

**Discussion of Part III.** In the effort to explain why any such relation from species to species, including even a "cold blooded" form, should exist, one must ponder the underlying conditions which determine heart rate, depolarization, repolarization and hence contraction. From mere in-

spection of the graph it is evident that mass of the heart is not the complete answer, for the QT values in turtle heart strips, intact turtles, elephants, dogs and medical students overlap at certain cycle values. If we consider, for example, Burnett and Taylor's<sup>7</sup> data for "reasonably healthy" young children, the younger the child the shorter is the QT. Also we

The frog and the elephant are seen to have the same metabolic rates; a man, a pig and a mare have similar rates. Thus it is seen that when 1 species is compared with another, weight and metabolism do not bear a constant relationship.

If the same data are rearranged according to decrease in metabolic rate, the order is:

TABLE 1.—RELATIONS OF ANIMAL WEIGHT, HEART RATE AND METABOLISM RATE

Species	Weight (gm.)	Heart rate (min.)	Calories (kg. per 24 hrs.)
Mouse . . . . .	1.75	700-1000	977
	12	670	639
	20	500	170
Frog . . . . .	25	30	13
Tortoise . . . . .	135	10-20	85
Guinea pig . . . . .	400	267	94
Hen . . . . .	1,000	354	110
Puppy . . . . .	1,750	180	110-150
Baby . . . . .	1,900	129	95
Hen . . . . .	2,000	300-350	71
Rabbit . . . . .	2,000	205	52
Cat . . . . .	2,500	116-128	79.5
Baby . . . . .	5,000	119	71
Dog . . . . .	9,600	96	40
Baby . . . . .	10,000	106	51
Goat . . . . .	33,000	135	49.5
Man . . . . .	66,000	55*	25
Calf . . . . .	115,000	...	37
Pig . . . . .	130,000	70-86	19
Percheron mare . . . . .	450,000	55	22
Ox . . . . .	500,000	24	43
Elephant . . . . .	3,600,000	20-50	13

\* This was the rate given in Clark's data, probably due to the special conditions of the study.

TABLE 2.—ANIMAL SPECIES ARRANGED ACCORDING TO DECREASING METABOLIC RATE

	Calories (kg. per 24 hrs.)		Calories (kg. per 24 hrs.)
1. Mice . . . . .	170-977	6. Ox, 500 kg. . . . .	43
2. Hen, 1 kg. . . . .	110	Dog, 9.5 kg. . . . .	40
Puppies, 2 kg. . . . .	100-150	Calf, 115 kg. . . . .	37
3. Guinea pig, 400 gm. . . . .	94	7. Man, 66 kg. . . . .	25
Baby, 2 kg. . . . .	95	Mare, 450 kg. . . . .	22
4. Cat, 2.5 kg. . . . .	79.5	Pig, 130 kg. . . . .	19
Hen, 2 kg. . . . .	71	8. Elephant, 3600 kg. . . . .	13
Baby, 5 kg. . . . .	71	Frog, 25 gm. . . . .	13
5. Rabbit, 2 kg. . . . .	52	9. Tortoise, 135 gm. . . . .	8.5
Baby, 10 kg. . . . .	51		
Goat, 33 kg. . . . .	49.5		

know that the younger the child the higher is the metabolic rate. Among the various species studied, mice are at one extreme with the highest metabolic rates and turtles at the other with very low rates. A tabulation from Clark<sup>9</sup> and from Benedict<sup>4</sup> presents this information with species arranged according to weight.

The numbers in Table 2 which indicate groups having similar metabolic rates also indicate the species order on the QT/cycle graph (Fig. 6) with such overlapping as one might expect. The suggestion is made that the QT to cycle relationship depends on cardiac oxygen consumption which in turn is a considerable factor in the so-

called "basal metabolic rate." The deviation of points from the "normal" line in any species is at least partly a measure of the change in cardiac cellular activity. Such an intracellular change would not necessarily be correlated with cardiac murmurs, hypertrophy, or any specific disease. One would expect it to vary temporarily because of changes induced by chemical or hormonal agents acting transiently (or experimentally as the result of electrical stimulation) (Moe *et al.*,<sup>18</sup> page 490); and to be permanently altered when such agents acted continuously or when some more or less permanent change in the cellular protoplasm had occurred.

Several well-known formulæ<sup>2,3,10,15</sup> are available to express this relationship. But why so many formulæ, why a difference between men, women and children, why one constant for youth and another for age? Possibly because there are too many variables, possibly because the variables already studied (mass, age, blood calcium, etc.) are not the ones which really determine the duration of QT. In other words the formulæ are inadequate because each requires a "constant" but we do not know what action or effect the constant represents, nor do we know that it represents 1 only.

Ruskin and Decherd<sup>25</sup> have studied electrical systole of the rabbit heart and conclude: "The QT-RR curves are obviously not linear." They have failed to consider that the "isolated perfused rabbit ventricle" artificially driven may be activated in entirely different sequence than is normal and that this sequence may be different at different rates either due to shift of electrodes with activity or due to different cellular metabolic states at extremes of rates. Moreover, they include very slow and very fast rates which are certainly abnormal for a rabbit heart; *c. g.*, as low as 50 per minute and above 400 per minute. One should remember that for each species there is a spread of heart rates and a limited range within the spread which can be taken as characteristic for a particular species. Let us complete the

quotation: "The QT-RR curves obviously are not linear, although in the central portion, excluding the slowest and fastest rates, the *deviation from linearity may not be great.*" Thus the data of Ruskin and Decherd<sup>25</sup> support Robb's opinion<sup>24</sup> that *within a range of rate normal for a given species* the QT-RR ratio is linear, although they came to a different conclusion. Schlamowitz<sup>26</sup> has already considered this matter and presented an analysis leading to the conclusion: "This curvilinear regression is not a better fit, statistically, than the linear regression."

If small areas of tissue are activated from one strand of "conducting" tissue, QT may be the time required for the depolarization and repolarization of such an island and QT would have the same duration whether 1 island or 1 million islands depolarized and repolarized, provided only all processes began and ended simultaneously. The fact that Blair, Wedd and Young's<sup>5</sup> turtle heart strips and White's elephant hearts<sup>28</sup> have QT intervals of similar duration could be interpreted in the sense that the "muscle strip" preparation is completely activated within a minimal time and that the multiple islands present in the elephant's heart are activated most efficiently. In larger hearts the "conducting" system is obviously longer and a longer time should be required for depolarization. But if depolarization of the conducting system does not register with ordinary electrocardiographic techniques (Ashman and Hull,<sup>2</sup> page 62; Bazett in MacLeod's *Physiology*,<sup>16</sup> page 284), if only surface effects register anyway, and if QT is a record of depolarization of ventricular muscle, then QT could not be expected to be longer merely because of longer conducting pathways, provided the individual islands of ventricular muscle to be depolarized in hearts of varying total size were of a similar area and as optimally connected, in large as in small hearts.

PR (or PQ) is the time elapsing from the first depolarization of auricular tissue (possibly the pacemaker but more prob-

ably auricular muscle) to the first depolarization of ventricular muscle itself (*not* the conducting system). Slowed conduction in the auricle, in the auriculo-ventricular connections, or a longer intraventricular pathway, would register as a delay in time between the onset of auricular and the onset of ventricular depolarization, that is, as a lengthened PR (or PQ) but not as a lengthened QRS or QT. This interpretation is substantiated by Ashman and Hull<sup>2</sup> (pages 69-70) and by Burch and Windsor<sup>6</sup> (page 63). PR varies with heart size.

Let us again quote from Ashman and Hull<sup>2</sup> (pages 69-70): "Those who have tried to interpret the human electrocardiogram in accordance with the newer view have been forced, in order to explain the normal width of the QRS complex, to assume that depolarization of a heart muscle fiber requires several hundredths of a second. If this be true, then conduction of the wave of excitation through ventricular muscle proper must be at an extremely low velocity, slower than in the turtle heart at much lower temperature." If we accept the view that QT is the time required for depolarization of a unit supplied by a single conducting strand, then in the intact heart a longer QT is due to some lack of simultaneity in the onset of depolarization and completion of repolarization of different units. We must not forget that if the wave of excitation did spread through any considerable extent of syncytium such a spread should have been detectable and this has not been the case either for normal hearts or for fibrillary waves.<sup>12,18</sup>

**PART IV. EXPERIMENTAL MODIFICATION OF QT.** *Method.* Some dogs were trained to lie in a cradle, on their backs, while epinephrine was given intravenously, either before or after administration of atropine. In other experiments dogs were given 30 mg./kg. of sodium pentobarbital after which the vagi were dissected and later were stimulated by electrodes leading from a Harvard Inductorium. Accelerator stimulation was performed before

and after atropinization. Electrocardiograms were recorded by crystal galvanometers built by the Cambridge Instrument Company. The paper speed was generally 50 mm. per second.

**Results.** By direct experimentation in intact dogs one can show that to a limited degree absolutely and to a great degree relatively QT is shortened by vagal stimulation. In addition we observed that if the heart cycle is long due to certain non-vagal causes (*e. g.*, moderate asphyxia in an atropinized animal) QT is long, whereas if the same cycle duration is caused by vagal stimulation (or by acetyl beta methyl choline) the QT is unduly shortened. QT/cycle ratios during vagal stimulation in 4 experiments are shown in Figure 7 B.

During accelerator stimulation the actual QT reading may remain constant, or may increase slightly or even decrease but the ratio of QT to cycle increases greatly (see Fig. 7 A). Epinephrine injection in unanesthetized dogs causes first a reflex vagal stimulation and later a mixed vagal and accelerator stimulation (see Fig. 8). If epinephrine is given after atropinization in unanesthetized trained dogs the QT changes are the same as when the accelerators are stimulated (compare Fig. 7 A with Figs. 8 and 9 G). One sees that if the proportion of vagal and accelerator influence is varied the QT duration will change even though the cycle is unchanged. Figure 9 A-B indicates that in trained dogs the QT/cycle ratio averages about 40. During anesthesia this ratio is higher, averaging 53. During vagal stimulation there is tremendous reduction of this ratio even to 9 or 10. The average for the whole period of vagal stimulation is 23 (Fig. 9 C). If the vagus is reflexly stimulated by the administration of epinephrine, the same marked reduction of QT/cycle occurs (Fig. 9 E). The QT/cycle ratio is shown for accelerator stimulations in Figure 9 D. After atropinization the ratio is raised above 60, averaging 65 (Fig. 9 F). When epinephrine is given after atropine (Fig. 9 G), the

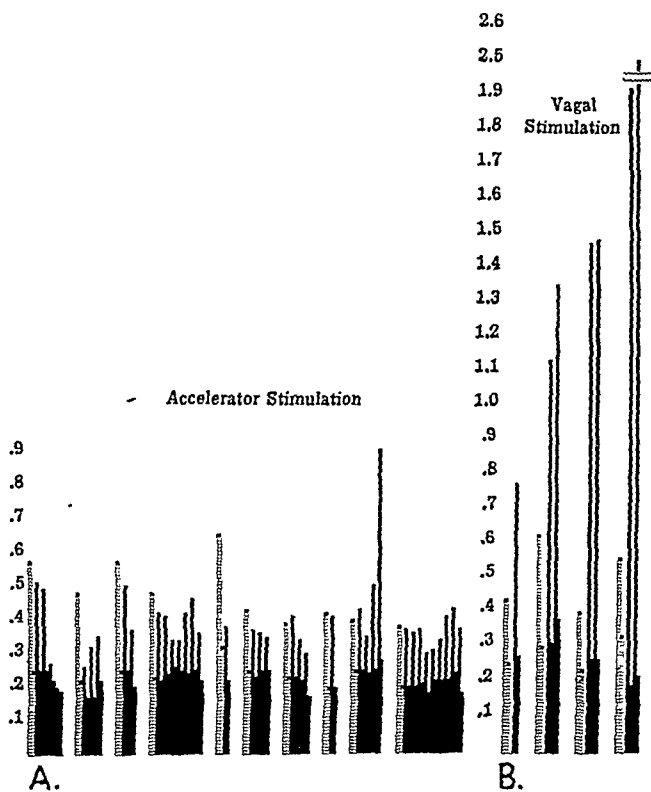


FIG. 7.—*A*, Accelerator stimulation in anesthetized dogs. Ordinates time in seconds. Taller columns represent cycle; following shorter columns are QT for same diastole. Cross-hatching control values, solid blocks result of stimulation. Data from 10 experiments. *B*, Vagal stimulation in anesthetized dogs. Results of 4 experiments. Times, cross-hatching and solid blocks have same significance as in 7 *A*.

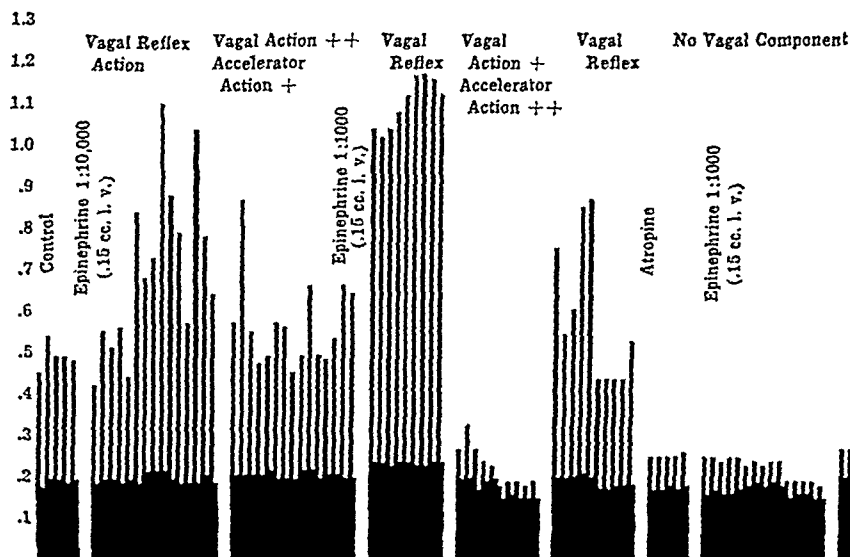


FIG. 8.—Data represent 1 experiment in a trained non-anesthetized dog, procedures indicated on graph. Comment in text. Ordinate represents time. Tall columns are cycle duration; following short columns are QT duration.

QT/cycle ratio becomes very high, even above 90.

**Summary and Conclusions.** 1. A "bundle of His" is present in the human fetal heart; this tissue merges imperceptibly (along a longitudinal axis) into heart muscle cells and a given strand supplies a limited area.

about the anatomic distribution of a conducting system to the ventricle. Because cutting and crushing experiments damage *all* tissues in this region, such procedures can never determine which tissue serves as a conducting pathway.

3. In accordance with the distribution of this differentially stained tissue and in

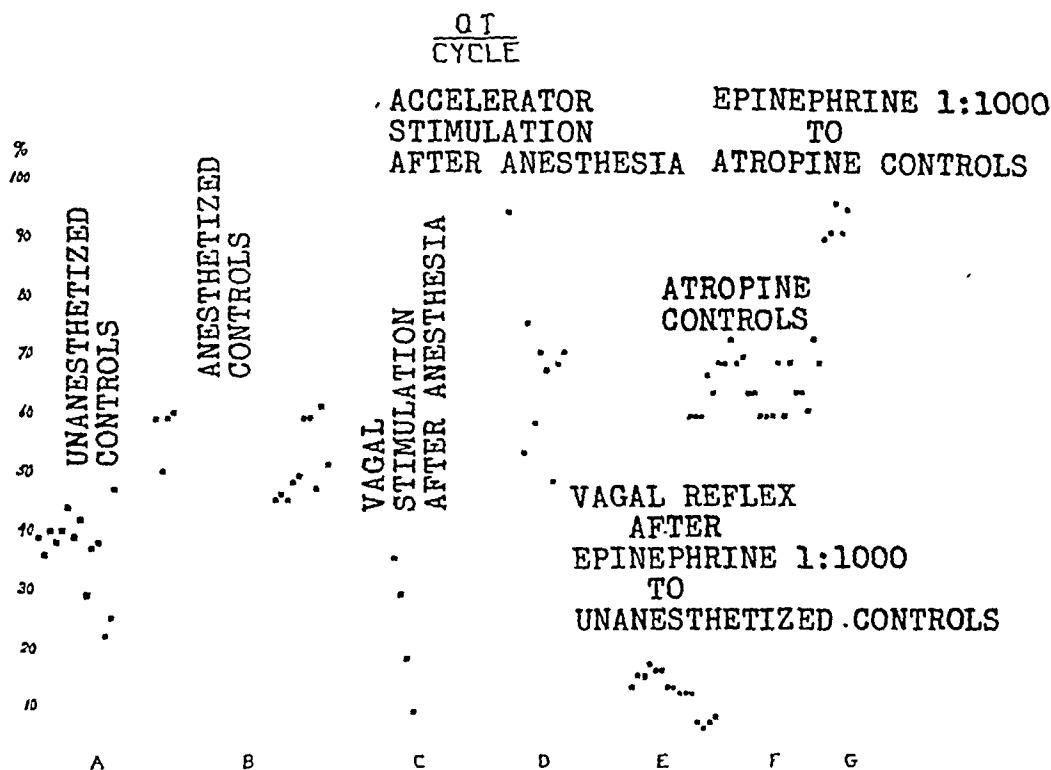


FIG. 9.—A scatter graph showing values of  $QT \div \text{cycle}$ , compiling the data in Figures 7 and 8.

2. The possibility exists that this structure, "similar in distribution to the 'bundle of His' and its ramifications in ungulates," is not the "conducting" system. If it is not, if conduction from auricle to ventricle is by way of nerves, then since no parasympathetic nerves reach the ventricular muscle (Nonidez) the sympathetic nerves would need to be the "conducting tissue." As yet no method has been devised for differential sympathetic staining and the ultimate distribution of these nerves to ventricular muscle is not known. In other words, if the structure "similar in distribution to the 'bundle of His' in ungulates" does not serve as the conducting pathway from auricle to ventricle, then we know nothing

in accordance with much data available in the literature regarding initial negativity of heart surfaces, it is suggested that quite limited areas of heart muscle, "islands," depolarize as a result of stimuli arriving over these numerous anatomic pathways.

4. QT readings for intact animals belonging to many species are presented and the relation of these to cycle length establishes that QT duration is independent of the total mass of the heart.

5. QT duration seems to be directly related to metabolism, presumably cardiac cellular metabolism.

6. In the intact dog, QT/cycle ratio is decreased by vagal stimulation.

7. In intact dogs, QT/cycle ratio is increased after atropinization and by accelerator stimulation.

8. Measurements of QT made under such conditions that the number of variables active at one time is limited offer an indication of the state of the heart muscle (*e. g.*, the effect of increased acetylcholine or epinephrine). Thus QT dura-

tion for a given cycle length can be varied at will.

9. The reason for lack of "clinical usefulness" of measurements of QT may be that the specific effects of all possible variables are not yet known.

10. In laboratory animals the QT/cycle ratio seems more significant than mere QT duration.

Grateful acknowledgment is made to the Hendricks Research Fund of this College and to the Life Insurance Medical Research Fund for financial aid. We also wish to thank Dr. Kaylor of the Department of Anatomy of the College of Medicine, Syracuse University, and Dr. Corner of the Carnegie Institute of Washington for the privilege of studying histologic sections prepared by them. In addition the data on unanesthetized trained dogs was taken from unpublished data of Dr. Allan Bass and William Murray of this department.

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## EFFECT OF THYROID HORMONE IN TISSUE RESPIRATION

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ALTHOUGH much progress has been made in the treatment of hyperthyroidism, its etiology remains obscure. It is not known by what mechanism the thyroid hormone accelerates the metabolic rate. Moreover, the structure of the thyroid hormone, in its active form, has not been determined, although it is believed that thyroxin constitutes part of this molecule. However, since the active hormone is largely concerned with oxidative phenomena, it seems important to know more about alterations in biologic oxidations in the body cells of thyrotoxic subjects and about compounds that will modify these reactions.

The amount of oxygen consumed ( $QO_2$ ) by many tissues of hyperthyroid animals has been stated to be increased, whether hyperthyroidism was produced by desiccated thyroid,<sup>10,11</sup> thyroxin,<sup>7,8,13,14,17,18,22</sup> or thyrotropin.<sup>21,22</sup> On the other hand, Gerard and McIntyre<sup>10</sup> found in thyroid-fed dogs that the  $QO_2$  of thyroid tissue was decreased. After thyroidectomy the oxygen consumption of the tissues was shown to be decreased.<sup>7,13</sup> Reiss and associates<sup>22</sup> stated that the amount of thyroxin that theoretically could be mobilized from the thyroid gland by giving thyrotropin to rats would be ineffective in producing increased tissue respiration when given parenterally in the form of thyroxin. This observation could be interpreted as indicating that thyroxin must become activated before it has a calorogenic effect.

Haffner<sup>12</sup> believed that in hyperthyroidism there is an increased anaërobic glycolysis and that the increased oxygen consumption in this condition resulted from the necessity of the organism to oxidize or resynthesize the increased metabolites.

However, results of the studies of these phenomena have varied.<sup>9,18,20,22</sup> In a thorough investigation of the subject, McEachern<sup>18</sup> concluded that an increase of tissue glycolysis is not the fundamental cause of the increased oxygen consumption in hyperthyroidism. He believed that there is no abnormal respiratory mechanism in the body cells. He found that hepatic and renal tissues from hyperthyroid animals oxidized various substrates (lactate, pyrovate and succinate) as well as did normal tissues, while muscle oxidized them at a rate greater than normal.

In this laboratory we have investigated some of these problems; the results are reported in this paper. The main objectives of these studies were to observe: (a) the direct and indirect effects of thyroglobulin or thyroxin on the oxygen consumption of tissue slices; (b) the effect of common inhibitors of respiration on tissues of normal and hyperthyroid animals; and (c) factors affecting the activation of thyroxin.

**Methods.** The experiments were performed with rats, guinea pigs and patients with thyroid disease. The rats were of the white Wistar strain and varied in size and sex; most of them were males weighing about 200 gm. They were fed Purina Laboratory Chow. The guinea pigs were of both sexes and varied in size, although most of them weighed about 300 gm. They were fed rabbit chow, supplemented with lettuce and carrots. Basal metabolism tests were conducted with a closed-circuit method, a small spirometer being used for each rat. The air was circulated by a vacuum pump. Carbon dioxide was removed with flakes of sodium hydroxide and water was removed by concentrated sulfuric acid. The test was



conducted after the animals had fasted for 18 hours. The basal metabolic rate was determined in the manner described by Lee.<sup>15</sup>

For the studies dealing with the oxygen consumption of tissue slices the animals were fasted for about 15 hours and were killed by a blow on the head. The liver, kidney, diaphragm, pectoral muscle, heart and thyroid gland were rapidly sliced into pieces less than 0.5 mm. in thickness. All of the tissue for each experiment was obtained from the same animal, except that thyroid tissue was taken from 2 or more animals. Duplicate sets of determinations, including control specimens, were conducted and the values were averaged.

The rate of oxygen consumption of these tissues was measured in Warburg respirometers containing either 3 cc. of Ringer's solution with 0.1% glucose and buffered with phosphate or 2.7 cc. of horse serum and 0.3 cc. of Ringer's phosphate-glucose solution. In the experiments with serum the bicarbonate was removed by shaking with hydrochloric acid at pH 6, after which the pH was adjusted to about 7.4 with sodium hydroxide. All of the horse serum used was obtained from the same bleeding and was kept in sterile ampoules at 5° C. In the center cup of each flask was placed 0.3 cc. of 20% potassium hydroxide. The manometers were flushed with oxygen for 10 minutes and were shaken at a rate of 100 to 120 oscillations per minute at 38° C. Readings were taken at intervals of 10 minutes for 1 or 2 hours and then the pH of the substrate was tested. The slices of tissue were removed from the flasks, rinsed in distilled water, dried at 105° C. for 24 hours and weighed. There was, on the average, about 15 mg. of water-free tissue obtained from each flask. The results were calculated in the usual way— $QO_2 = \text{c.mm. } O_2 \text{ consumed per hour per mg. dry weight of tissue}$ . Except where stated otherwise, the values are based on the oxygen consumption during the 1st hour.

Thyroglobulin was prepared in the manner described by Canzanelli and Rapport.<sup>1</sup> It contained about 0.7% iodine. In dry form it remained active for several months. Preceding each experiment with thyroxine, the crystals were dissolved in saline with the aid of a very small amount of 1N sodium

hydroxide. The thyrotropic hormones\* used in these studies was found to have 50 Junkmann-Scholler units of thyroid activity per 1 cc. of solution.

The remaining details of the methods used are described in conjunction with the report of the results of the experiments.

**EFFECT OF THYROGLOBULIN.** Thyroglobulin was found to increase the  $QO_2$  of guinea pig and rat liver. In 6 of 7 experiments using horse serum as the substrate, the  $QO_2$  of guinea pig liver was increased from 40 to 100%, as noted in Table 1. In the 4 experiments using rat liver and horse serum, the percentile increase in  $QO_2$  varied from 30 to 37%. In each of 5 experiments using guinea pig or rat liver suspended in a medium of Ringer's phosphate-glucose solution, thyroglobulin produced a significant increase in the oxygen consumption (Table 1). In the 1 instance when the serum of a patient with hypometabolism, but not hypothyroidism, was used in conjunction with thyroglobulin, no increase in the  $QO_2$  was observed. It is to be noted that no increase in oxygen consumption of diaphragm or kidney occurred during the 1st hour of incubation, but there was a significant increase in the 2nd hour.

On the basis of these results and the experiences of others, it is clear that thyroglobulin increases the  $QO_2$  of many tissues. Therefore, it is important to know how this substance is related to the circulating hormone. Upon using a delicate test for thyroglobulin, Lerman<sup>16</sup> failed to demonstrate the presence of this substance in the blood stream, except after traumatization of the thyroid gland as during thyroidectomy. DeRobertis<sup>6</sup> postulated that a proteolytic enzymatic action in the thyroid gland leads to a disintegration of thyroglobulin, permitting the entrance of a smaller molecule, like thyroxine, into the blood stream. However, as illustrated by the following results as well as experiences of others,<sup>3,4</sup> it seems necessary for thyroxine to undergo

\* Thyrotropic hormone (Antuitrin-T) was furnished through the courtesy of Dr. Oliver Kamm, Parke-Davis and Company, Detroit, Mich.

some process of activation before it can increase the rate of oxygen consumption of tissues.

**EFFECT OF THYROXIN.** Although thyroxin, when injected intravenously, causes a prompt and pronounced increase in the basal metabolic rate, many investigators have observed that this compound causes little or no increase in the  $QO_2$  when it is added directly to tissues in Warburg respirometers.

in thyroxin or in body fluid or tissue before this compound can increase the rate of biologic oxidations. Such a change can take place within 6 hours *in vivo*, as shown in Figure 1. From each of 3 myxedematous patients serum was withdrawn for use as a control and then thyroxin in doses of 3, 5, or 12 mg. was administered intravenously. Four samples of serum from each of the 3 patients were obtained within the next 12 hours. Certain speci-

TABLE 1.—EFFECT OF THYROGLOBULIN ON  $QO_2$  OF GUINEA PIG AND RAT TISSUES

Substrate	Guinea pigs		Rats	
	Amount of thyroglobulin (mg.)	Increase $QO_2$ (%)	Amount of thyroglobulin (mg.)	Increase of $QO_2$ of $QO_2$
	Slices of liver		Slices of liver	
Horse serum . . . . .	5.0	40	5.0	57
	5.0	0	5.0	30
	5.0*	100	10.0	38
	5.0*	93	10.0	50
	10.0	50		
	10.0	57		
	10.0	63		
Hypometabolism† . . . . .	10.0	0	5.0	100
Ringer's phosphate-glucose . . .	2.5	30	50.0‡	120
	10.0	44	5.0§	48¶
	100.0	55	5.0	111¶

\* The thyroglobulin used in this experiment was prepared from a thyroid gland of man.

† The serum was obtained from a patient with hypometabolism but not hypothyroidism.

‡ Slices of kidney.

§ Slices of diaphragm.

¶ Oxygen consumption during the 2nd hour of incubating. No significant change in  $QO_2$  took place during the 1st hour.

We found that the addition of thyroxin to liver slices caused no increase in the  $QO_2$  during the 1st hour. Canzanelli, Guild and Rapport<sup>3</sup> found in most of their experiments that thyroxin had no stimulating effect. With thyroid tissue, Paal<sup>21</sup> found increases of 200% when it was suspended in serum and thyroxin for a period of 24 hours. Davis, DaCosta and Hastings<sup>4</sup> observed that thyroxin *in vitro* increased the tissue. Moreover, the increase in respiration of the frog heart did not occur until after several hours of incubation. Davis and Hastings<sup>5</sup> found that thyroxin increased the oxygen consumption of the excised limulus heart after incubation for 15 hours.

*Rate of Activation of Thyroxin in Vivo.* Some change probably takes place either

of the serum added to slices of guinea pig liver in Warburg respirometers caused a distinct increase in the  $QO_2$ , the maximal response being obtained with serum withdrawn about 6 hours after the patients had received thyroxin. In the 2 patients who received the smaller doses of thyroxin, after 12 hours the effect of the serum was not much different from that obtained before these patients received thyroxin. Serum withdrawn 6 days after 1 patient had received 12 mg. of thyroxin yielded the same  $QO_2$  as did pre-treatment serum. In a fourth myxedematous patient serum obtained 50 hours after the subject had been given 7 mg. of thyroxin gave the same results as serum obtained from this subject before treatment. These observations suggest that thyroxin does

become activated in the body within a few hours, but the site of activation is not known. Not much hyperactivity was demonstrated by the serum after 12 hours. The thyroid gland apparently did not participate in the reaction in these myxedematous patients since there was essentially no thyroid tissue present. The following experiments were conducted to determine whether thyrotropin, normal serum or liver tissue might affect the activation of thyroxine.

was added to 2.7 cc. of serum and slices of guinea pig liver. No calorigenic effect was observed, although in a similar experiment 0.1 mg. of thyroglobulin caused a 33% increase in  $QO_2$ .

*Experiment III:* Thyroxine + Antuitrin-T + serum were added to rat liver and the  $QO_2$  was determined immediately thereafter. The rate of respiration was the same as without the hormones. The same results were obtained when guinea pig liver was used instead of rat liver.

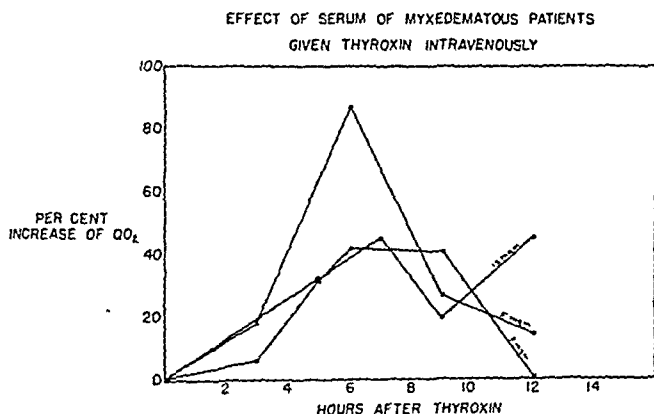


FIG. 1.—Note that serum obtained 3 hours after the injection of thyroxine caused a slight increase in  $QO_2$  of liver slices, but the maximal effect was obtained after 6 to 9 hours. The larger the dosage of thyroxine the greater was the calorigenic action of the serum at 12 hours.

*Is Thyroxine Activated by Serum and Thyrotropin?* *Experiment I:* In this experiment the following solutions were measured out: (a) 0.9 cc. serum + 0.1 cc. (0.2 mg.) of thyroxine, (b) 0.9 cc. of Antuitrin-T + 0.1 cc. of thyroxine, (c) 0.5 cc. of Antuitrin-T + 0.4 cc. serum + 0.1 cc. thyroxine, (d) 0.9 cc. saline + 0.1 cc. of thyroxine, (e) 0.5 cc. of Antuitrin-T + 0.5 cc. of serum, and (f) 1 cc. of serum. The solutions were incubated at  $38^\circ C$ . for 5 hours and then 0.3 cc. of each was added to 2.7 cc. of horse serum containing slices of rat liver or heart. In no instance was thyroxine found to have a calorigenic effect.

*Experiment II:* One cc. (2 mg.) of thyroxine and 2 cc. of Antuitrin-T, pH 6.8 were incubated at room temperature for 48 hours. Then 0.3 cc. of the mixture

*Is Thyroxine Activated by Serum and Liver?* To 10 mg. of thyroxine, dissolved with 1 drop of normal sodium hydroxide, was added 10 cc. of serum. About 7.5 cc. of this mixture was incubated at  $37^\circ$  for 15 hours with 45 mg. of guinea pig liver slices and the other 2.5 cc. was incubated without liver. The liver slices were removed and the volume of the solution was increased 3 times with phosphate medium. An aliquot of 3 cc. was placed in respirometers in the presence of slices of fresh guinea pig liver. However, no calorigenic effect was observed.

Ten mg. of thyroxine, dissolved with 1 drop of sodium hydroxide, was added to 10 cc. of serum and an aliquot, 1.5 cc. was incubated with 21 mg. of guinea pig liver slices. Similar amounts of thyroxine-serum mixture without liver, and plain serum were incubated simultaneously at

37° for 48 hours. The liver tissue was removed and the solutions were diluted 10 times with phosphate medium and 3 cc. were used in the respirometers with liver slices. The  $QO_2$  of the specimen incubated with liver was 300% greater than the 1 containing serum only.

In 6 similar experiments there was no increase in the  $QO_2$  when the substrate contained thyroxin that had previously been incubated with serum (Table 2). However, when thyroxin was incubated with liver slices and serum, an increase in  $QO_2$  occurred in 2 of the 6 experiments. No increase in  $QO_2$  resulted when the incubation mixture consisted of serum and liver without thyroxin or when serum alone had been incubated for 48 hours. Moreover, when phosphate medium was incubated with or without thyroxin it led to no increase in  $QO_2$ .

port,<sup>2</sup> who also found that when thyrotropin plus either thyroxin, thyroglobulin or diiodotyrosine were incubated with either thyroid or liver, the effects produced were additive ones of each of the test materials separately. These investigators concluded that the action of thyrotropic hormone on metabolism, through the thyroid, was not due to a specific effect on thyroxin, thyroglobulin or diiodotyrosine. Although thyrotropin stimulates thyroid cells *in vitro* as well as *in vivo*, the  $QO_2$  of thyroid tissue is not necessarily proportional to the amount of hyperplasia that develops.<sup>23</sup>

EFFECT OF SERUM OF PATIENTS WITH SIMMONDS' DISEASE, MYXEDEMA OR THYROTOXICOSIS. When normal horse serum was used as the substrate, the  $QO_2$  of liver tissue was higher than when Ringer's phosphate-glucose was used (Table 4)

TABLE 2.—INCUBATION OF THYROXIN WITH SERUM AND LIVER TISSUE

Hours of incubation	Tissue (mg.) (dry weight)	$QO_2$				
		Control	Thyroxin + serum	Increase (%)	Thyroxin + serum + liver	Increase (%)
24 . . .	5.8	4.6 + 0.1	4.3 + 0.0	0	4.3 + 0.1	0
	9.7	5.6 + 0.1	5.4 + 0.1	0	5.5 + 0.1	0
	11.9	5.5 + 0.4	5.0 + 0.3	0	7.0 + 0.6	45
48 . . .	9.7	5.3 + 0.1	5.7 + 0.2	0	34.0 + 2.0	507
	7.2	5.1 + 0.3	5.0 + 0.1	0	5.6 + 0.2	0
	10.1	5.4 + 0.0	4.8 + 0.6	0	5.4 + 0.1	0

As to why thyroxin, incubated with liver and serum appeared to have become distinctly activated in 3 experiments and not in the other 4 is not known. It is possible that the liver and serum mixture might have the capacity of inactivating thyroxin as well as of activating it.

EFFECT OF THYROTROPIC HORMONE. Two-tenths of 1 cc. of thyrotropic hormone (Antuitrin-T), added to serum containing slices of liver, heart, diaphragm or thyroid, caused no increase in the respective  $QO_2$  (Table 3). There was no increase in  $QO_2$  when thyroxin (0.2 mg.) and thyrotropin (0.2 cc.) were added to liver slices, nor when thyrotropin, thyroid tissue and liver tissue were incubated together. These observations are in accord with those of Canzanelli and Rap-

However, there was no essential difference in the  $QO_2$  of liver or heart whether the serum used was from a horse or a normal, thyrotoxic, myxedematous, or panhypopituitary individual. The respiration of diaphragm or pectoral muscle was the same with the serum of either a normal or thyrotoxic subject. The respiration of thyroid tissue varied in different experiments, but the results of individual tests demonstrated that the respiration was less in the presence of serum of patients with thyrotoxicosis than it was with serum of normal man or horse. Whether this decreased  $QO_2$  was related to the increased amount of thyroid hormone in the serum is a matter of conjecture.

Biopsies were performed on the gastrocnemius muscles of 4 patients, 2 of whom had myxedema, 1 Simmonds' disease and

1 thyrotoxicosis. Only local anesthesia was used and care was taken to avoid getting novocaine in the muscle. Slices of myxedematous muscle were incubated with the sera of normal, thyrotoxic and myxedematous subjects. The  $QO_2$  was essentially the same in each case. The muscle slices of the patients with Simmonds' disease or thyrotoxicosis had distinctly lower  $QO_2$  values in the serum of patients with Simmonds' disease or the serum of thyrotoxic subjects than in normal serum.

each of the inhibitors was administered to rats, intraperitoneally in from 0.1 to 0.5 cc. of saline. Each of the rats weighed from 135 to 165 gm. Death occurred in 1 minute after 0.4 mg. of cyanide, after 4 minutes with 0.8 mg. of azide, after 18 minutes with 20 mg. of moniodoacetate, after 25 minutes with 200 mg. of malonate and after 46 minutes with 5 mg. of fluoride.

Three experiments were conducted with rats in which the inhibitors were given in the drinking water for 6 days or longer.

TABLE 3.—EFFECT OF THYROTROPIN (ANTUITRIN-T) ON THE  $QO_2$  OF GUINEA PIG TISSUE

Tissue	No. experiments	Control	No. experiments	Thyrotropin (0.2 cc./flask)
Liver . . . . .	22	7.6	3	7.6
Heart . . . . .	17	5.9	3	5.9
Diaphragm . . . .	6	3.7	3	3.3
Thyroid . . . . .	8	5.6	3	4.8

TABLE 4.—EFFECT OF TYPE SERUM ON  $QO_2$  OF GUINEA PIG TISSUES

Tissue	Substrate	No. experiments	Average $QO_2$
Liver . . . . .	R.P.G.*	4	4.2
	H.S.	22	7.6
	N.S.	13	7.5
	T.S.	14	8.5
	M.S.	5	7.3
	S.S.	4	6.8
Heart . . . . .	H.S.	17	5.9
	N.S.	8	7.2
	T.S.	8	5.6
	M.S.	2	5.0
	S.S.	4	5.7
Diaphragm . . . .	H.S.	6	3.7
	N.S.	3	2.6
	T.S.	8	2.9
Pectoral muscle . . . .	T.S.	4	2.4
	T.S.	2	2.5

\* R.P.G., Ringer's phosphate-glucose; H.S., horse serum; N.S., normal serum (man); T.S., serum of patients with thyrotoxicosis; M.S., serum of patients with myxedema; S.S., serum of patients with Simmonds' disease.

**EFFECT OF ENZYME INHIBITORS.** Five common enzyme inhibitors were studied. The experiments were divided into 2 main groups: the inhibitor was given in the drinking water of rats in 1 instance and in the other it was added to the substrate in Warburg respirometers.

*In Vitro Studies.* The dosages of the inhibitors were selected after conducting preliminary tests of the approximate lethal dosages, as illustrated by the following examples. The sodium salt of

*Experiment I:* Five groups of rats, with 3 in a group, each rat weighing from 130 to 190 gm., were given an inhibitor in the drinking water in the amounts listed in Table 5. After 6 days the basal metabolic rate was determined, the animals were killed with a blow on the head, and in some instances estimations of the  $QO_2$  of the liver and heart were made.

On comparing the basal metabolic rates of these animals with those of animals of the same size and sex it was found

(Table 5) that the rate had increased in each group of rats, with the exception of the 1<sub>1</sub> receiving fluoride. With cyanide, azide and iodoacetate the increase was 50% or more. The  $QO_2$  of liver slices was significantly decreased with cyanide and iodoacetate, but was essentially unchanged with azide and malonate, whereas the  $QO_2$  of heart slices was decreased with malonate and iodoacetate, but increased with azide.

creased significantly in each group, the increase being greater in the ones which received thyrotropin plus an inhibitor, except in the group given azide. There was no decrease in the  $QO_2$  in any of the 4 groups tested. In fact, there was an increase in the  $QO_2$  of liver slices in the groups which received fluoride or azide.

*Experiment III:* This experiment was similar to the preceding one. There were

TABLE 5.—EFFECT OF INHIBITORS ON BASAL METABOLIC RATE AND  $QO_2$  IN RATS

Inhibitor	Drinking waters (%)	B.M.R. (%)	$QO_2$ (%)	
			Liver	Heart
Cyanide . . . . .	0.25	+60	-35	
Fluoride . . . . .	1.25	0		
Azide . . . . .	0.12	+50	0	+27
Malonate . . . . .	0.40	+25	0	-28
Iodoacetate . . . . .	10.00	+54	-24	-15

\* Each inhibitor was in the form of its sodium salt.

TABLE 6.—EFFECT IN 10 DAYS OF INHIBITORS AND THYROTROPIN ON THE GROWTH AND BASAL METABOLIC RATE OF RATS AND THE  $QO_2$  OF THEIR LIVER

Inhibitor	Dose* of inhibitor (mg./rat)	Weight gain (%)		Increase in B.M.R. (%)		Increase in $QO_2$ (%)	
		Inh.	Inh. + TTH†	Inh.	Inh. + TTH	Inh.	Inh. + TTH
Cyanide . . . . .	0.1	68	32	30	45	4	6
Fluoride . . . . .	0.5	55	61	15	45	39	19
Azide . . . . .	0.1	82	66	55	30	21	70
Iodoacetate . . . . .	2.0	53	..	45			
Malonate . . . . .	50.0	75	50	4	64	0	13

\* Daily dose of inhibitor (inh.) given subcutaneously in 0.2 cc. of saline.

† TTH, thyrotropin (Antuitrin-T)—0.1 cc. given subcutaneously once daily.

Microscopic sections of the liver, muscle and thyroid of some of these animals revealed no abnormalities with the exception of slight hyperplasia of the thyroid in the animals receiving cyanide or malonate. In the latter there also was decreased colloid and greater vacuolization than normal.

*Experiment II:* In this experiment 18 rats, weighing from 33 to 40 gm. were divided into 9 groups. Once daily each animal in 5 groups was given, subcutaneously, 0.2 cc. of 1 of the 5 aforementioned inhibitors in concentrations listed in Table 6. Each of 4 other groups was given daily injections of thyrotropic hormone, 0.1 cc., and 1 of the inhibitors. After 10 days all rats had gained weight, but less rapidly than did normal control animals. The basal metabolic rate in-

10 groups of rats with 2 animals in each group. These rats had an average initial weight of about 75 gm. They were given the same inhibitors and thyrotropin in the same dosage as in the previous experiment. After 8 and 14 days there was no decrease of the basal metabolism, but there was not as much increase as in the previous experiment. Again there was a distinct inhibition of weight gain.

Sections of the thyroid and liver of each of the animals were examined microscopically. There were no remarkable abnormalities in the liver and no hyperplasia of the thyroid except in the groups receiving thyrotropin.

It is clear that with the doses of inhibitors used no decreased basal metabolic rate was produced in rats. However, that some inhibitory effect probably took place

is indicated by the decreased  $QO_2$  that was observed in some instances. The increase in the intact animal was probably related to a variability in the response of different tissues to the inhibitors with an inefficient metabolism resulting.

*In Vitro Studies.* The effects of cyanide, fluoride, malonate, azide and iodoacetate on the  $QO_2$  of slices of liver, heart and diaphragm of hyperthyroid guinea pigs were tested. The hyperthyroidism was produced by the injection of thyrotropin daily for several days preceding the test. The concentration of the inhibitors used in the Warburg vessels was either 0.02 or 0.04 M. Iodoacetate was also tested in concentrations of 0.002 and 0.004 M. In 1 experiment 50 mg. of thyroglobulin was added to slices of liver of normal animals and the inhibitory effect of iodoacetate was tested.

The amount of inhibition of cyanide was about 85%, of iodoacetate 40%, of fluoride 35% and of malonate and azide 30%. Similar degrees of inhibition were observed with slices of liver, heart and diaphragm of normal guinea pigs.

These observations are in keeping with those of McEachern,<sup>18</sup> who concluded that cyanide, fluoride and moniodoacetic acid reduced the respiration of hyperthyroid tissues, but did not affect the fundamental mechanism which makes an increased supply of oxygen necessary to the organism. Gordon and Heming<sup>21</sup> found that fluoride or cyanide caused the same percentage decrease in  $QO_2$  of both normal and hyperthyroid liver slices, and malonate produced equal  $QO_2$  values. These investigators found that malonate caused marked inhibition in the respiration of hyperthyroid rat diaphragm but no change in the normal tissue.

*Discussion.* Neither the precise structure of the thyroid hormone nor its site of action has been demonstrated. However, sufficient data have been accumulated to permit reasonable tentative hypotheses. Since (a) proteolytic action on thyroglobulin antecedes its liberation from the thyroid gland;<sup>6</sup> (b) thyroglobulin ap-

parently does not usually circulate in the blood stream;<sup>16</sup> (c) thyroxin, unlike thyroglobulin, does not exert a calorogenic effect on tissue slices for several hours; and (d) thyroxin polypeptide promotes a distinct stimulation of the basal metabolic rate whether given orally or intravenously,<sup>19</sup> it is possible that thyroxin exerts most of its calorogenic action in the form of a peptide. If thyroxin polypeptide is the active form of the thyroid hormone, it may be asked where is the site of conjugation when thyroxin is administered to a thyroidless individual. Apparently the liver possesses this capacity; whether there are other sites is not known. Thyrotropin caused no activation of thyroxin.

It is of especial interest that some of the common inhibitors of respiratory enzymes, when given to intact animals, did not produce a lowering of the basal metabolic rate, but promoted hypermetabolism. Since the same compounds, when added to slices of tissues, caused a pronounced inhibition of oxygen consumption, it seems reasonable to conclude that with the dosages used there was a variation in the response of the tissues, the inefficiency in function of some tissues leading to hyperfunction of others. The situation might be compared to animals with marked thiamine deficiency in which the  $QO_2$  of certain tissues is reduced, but the basal metabolic rate is increased. These observations raise the question, which has often been considered in the past, as to whether hyperthyroidism is a compensatory reaction to an altered metabolic state in the tissues.<sup>2,3</sup>

*Summary.* Studies were made of the effects of thyroglobulin, thyroxin and thyrotropin on the oxygen consumption of tissues of rats, guinea pigs and patients with alterations in thyroid function. Investigations of the effects on these tissues of serum of normal subjects and of patients with thyrotoxicosis, myxedema or Simmonds' disease were also made. Studies of the effects of common respiratory enzyme inhibitors were made in normal and hyperthyroid animals.

Although thyroglobulin usually caused a prompt increase in  $QO_2$  when added to slices of tissue, thyroxin rarely had any such effect, either alone or in conjunction with thyrotropin. In a few instances, when thyroxin was incubated with liver slices and serum for 1 or 2 days and then the solution was added to fresh tissue, a distinct increase in  $QO_2$  resulted. The fact that other similar experiments demonstrated no effect with thyroxin suggested that the same medium might activate and inactivate thyroxin.

In 1 series of experiments thyroxin was injected, intravenously, into 3 patients with myxedema and 4 specimens of serum were obtained during the next 12 hours. In each patient the serum acquired the capacity to increase the  $QO_2$  of slices of guinea pig liver. The maximal effect was obtained about 6 hours after the injection of thyroxin and thereafter it tended to disappear. Thyrotropin was not found to increase the  $QO_2$  of slices of liver, heart, diaphragm or thyroid. When serum of a normal man or horse was used as a substrate with slices of tissue a

higher  $QO_2$  was obtained than when Ringer's phosphate-glucose solution was used. There was no essential difference in the  $QO_2$  of heart or liver tissues whether the serum used was from a normal, thyrotoxic, myxedematous or panhypopituitary individual.

Whether slices of muscle of myxedematous patients were incubated with sera of normal, thyrotoxic or myxedematous subjects, the  $QO_2$  values were essentially the same.

The sodium salts of cyanide, fluoride, azide, malonate and iodoacetate, administered to rats for several days, caused an increase in the basal metabolic rate and an inhibition of growth. The  $QO_2$  values of liver slices were increased in most instances, but decreased in a few. However, each of the compounds, when added to Warburg respirometers containing slices of liver, heart or diaphragm from normal or hyperthyroid animals, caused a distinct decrease in  $QO_2$ .

Further studies on the site and mechanism of action of the thyroid hormone are in progress.

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# PROGRESS OF MEDICAL SCIENCE

## SURGERY

UNDER THE CHARGE OF

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### VAGOTOMY FOR PEPTIC ULCER

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DURING the past 20 years there have been many changes in viewpoint with regard to the therapy of peptic ulcer by surgical means. The most common operations performed years ago for the treatment of duodenal ulcer were simple gastro-enterostomy and pyloroplasty. In the early 30's an increasing number of partial gastrectomies were performed, and until recent years partial gastrectomy has been the operation of choice for the treatment of duodenal ulcer. The transition in popularity from gastro-enterostomy to partial gastrectomy was due primarily to the high incidence of gastrojejunal ulcers following gastro-enterostomy. The removal of a fair portion of the acid-producing area of the stomach tended to reduce the number of jejunal ulcers, and while the incidence is lower following adequate partial gastrectomy, this latter procedure is not insurance against their occurrence. Many have objected to partial gastrectomy on the basis that it is a mutilating operation which sacrifices a considerable amount of the stomach.

In 1943 Dragstedt and his associates<sup>16</sup> performed bilateral resection of the vagus nerves as a means of decreasing the excess secretion of acid seen in ulcer patients. Since practically all methods of treatment of duodenal ulcer are based on control of acid in the stomach or its diversion from the duodenum, resection of the vagus nerves has been received with enthusiasm, not only because it is well known that stimulation of the vagus nerve increases acidity in the stomach and resection of these nerves causes a decrease in acid secretion, but also because of the simplicity of the procedure. As might be expected, bilateral resection of the vagus nerve below the lower border of the bifurcation of the trachea is not a new procedure. This operation has been frequently proposed and there is a record of the operation having been performed in 1911.<sup>20</sup> Since this time the operation has been performed for gastric crisis as well as for peptic ulcer, but as a method of therapy for either disease the operation was discontinued. Experimental work has

been carried on in relation to the effect of the vagus on gastric acidity since 1904.<sup>14</sup>

In 1900 Jaboulay<sup>33</sup> extirpated the celiac plexus and Mingazzini<sup>47</sup> divided the posterior nerve roots intradurally for relief of gastric crises in *tabes dorsalis*. The object of this operation was the control of pain. It was not until Foerster<sup>21</sup> developed a procedure similar to Mingazzini's that Exner, in 1911,<sup>20</sup> attempted to simplify the Foerster operation, by dividing the vagi subdiaphragmatically in a manner almost identical to the Dragstedt<sup>15</sup> procedure of today. He noted atony of the stomach and performed a gastrostomy over a tube passed through the pylorus into the duodenum to correct this condition. Later he performed a gastro-enterostomy in addition to the vagotomy. Bircher, in 1920,<sup>7</sup> reported favorably on vagotomy, but his indication for the operation, like Exner's, seemed to have been *tabes* or any "obscure gastropathy" as only 1 of his cases had ulcer. Latarjet<sup>40</sup> first reported on this procedure in 1922. He sectioned the vagal filaments in the abdomen after the main trunks had divided and applied the procedure to *tabes*, peptic ulcer and "obscure gastropathy." He makes the same claims for the procedure as are made today. He felt it was indicated in cases of peptic ulcer without obstruction and in more than half of his cases he added gastro-enterostomy. He remarked that following the operation alimentation was normal, the patients gained weight, had an immediate sense of well-being, and considered themselves cured. In all, Latarjet,<sup>40</sup> Wertheimer,<sup>41</sup> Pauchet<sup>52</sup> and Gianolla<sup>24</sup> reported 59 cases, in 18 of which they had done vagotomy alone. Giordano,<sup>25</sup> Stierlin<sup>60</sup> and undoubtedly others have also used the procedure but the record of their work is not now accessible.

Borchers,<sup>8</sup> in 1921, and Koennecke,<sup>37</sup> in 1922, reviewed the work on vagotomy for the preceding 11 years. Although they accepted the seemingly favorable results obtained, they objected to the operation on the theoretical basis that cutting the

nerve supply to the stomach, gall bladder, small bowel and half of the colon for disease of the stomach and first part of the duodenum was not justified.

Laignel-Lavastine<sup>39</sup> reviewed the literature in 1924 and commented favorably on the future of vagotomy, and Eiselberg,<sup>19</sup> in 1925, predicted that the more radical procedure of gastrectomy would some day be replaced by vagotomy.

Schiassi,<sup>56</sup> in 1925, reporting on 26 cases of duodenal ulcer, had done vagotomy alone in 11 cases, and vagotomy plus gastro-enterostomy in 15 cases. He did the Latarjet procedure which consisted of division of the vagus nerves below the diaphragm and added to it an incision which circumcised the outer layers of the gastric wall at about the junction of the proximal and middle thirds. He seemed enthusiastic about this procedure also. Pieri,<sup>53</sup> in 1932, reported 14 cases in which infradiaphragmatic vagotomy was performed. He described sectioning both main trunks beneath the diaphragm for peptic ulcer. At the time of his report he had done 6 vagotomies without gastro-enterostomy and stated that he doubted the necessity for the latter procedure.

We are unable to find any record of an unfavorable report concerning this operation. Pieri<sup>53</sup> has reported that secretion and motility in some of his cases returned to normal within a matter of months, but he does not offer the results of these studies as argument against the procedure. We could find no report of a recurrent ulcer following vagus resection. We might suppose that knowledge of the operation was not widespread, as Pieri in 1932 credits only Exner and Giordano with having previously performed bilateral vagotomy.

At about this time, however, the procedure of gastro-enterostomy and pyloroplasty were being superseded by gastrectomy and the surgical attention seems from 1920 on to have been focused on this operation with its many variations to the exclusion of vagotomy. Even those who in that day considered gastrectomy a "mutilating, unphysiologic procedure" were

not raising their voices in defense of vagotomy and the operation received no mention in standard surgical textbooks of the time.

C. H. Mayo,<sup>44</sup> in 1928, did several selective vagotomies evidently for the lesion of pylorospasm. He sectioned the gastrohepatic omentum above the distal stomach and proximal duodenum and in that way deprived these tissues of their vagal supply.

It is to be pointed out in consideration of the older attempts at vagotomy, that the type of operation was quite varied and in most instances there is doubt that the entire vagus innervation of the stomach was resected. Surely attempts at resection of filaments on or within the stomach wall cannot be considered as complete vagotomy since in some instances the resection was performed in the mid-portion of the stomach and did not resect the nerve high enough to cause much effect upon acid secretion. There is but 1 report which appears to us to have approached the problem in a manner which might be considered as adequate. Pieri<sup>53</sup> performed subdiaphragmatic vagotomy by exposing the lower end of the esophagus and sectioning the 2 main vagal trunks. This procedure appears to be similar and just as complete as that done today. There is no question that the basic concept was that resection of the vagus nerve might vary the course of a peptic ulcer. However, there is no doubt that the effects of vagotomy were not clearly understood until the careful work of Dragstedt and his associates<sup>16</sup> in 1943.

Since atropine, which has had an important and time-honored place in the treatment of peptic ulcer, acts by paralyzing the vagal end-organ, one might say that there has been a wealth of clinical experience with vagotomy. Rokitansky,<sup>55a</sup> in 1841, however, seems to have been the first to describe ulcer of the stomach as "due to morbid condition of the vagus and to the extreme acidification of the gastric juice." This idea has been expressed many times since by Arndt,<sup>1</sup> Beneke,<sup>5</sup> Hart,<sup>29</sup> Hoffman,<sup>21</sup> Roessle,<sup>55</sup> von Winiwarter,<sup>67</sup>

and others. Some of the opinions or studies have been made on the basis of observed association between cerebral neoplasm or birth injury to cerebrum, on the one hand, and ulceration of the stomach or melena neonatorum, on the other. Wilks,<sup>71</sup> in 1889, in questioning the rôle of the vagus, stated that ulcer of the stomach could be considered neurotrophic just as we have neurotrophic corneal ulcer, and von Bergmann,<sup>65</sup> in 1913, emphasized that the parasympathetic system is disordered in ulcer; that these patients respond more readily to pilocarpine; and that the long-continued use of atropine will therefore either cure or ameliorate the disease.

Cushing,<sup>13</sup> in 1932, again advanced the theory of the neurogenic origin of peptic ulcer. He makes the interesting point that only man of all animals develops ulcer spontaneously and that the incidence of the disease is increasing with the increasing stress of modern living. This coincidence is striking in itself; but, as evidence of central nervous system involvement in peptic ulcer, he reported his unusual experience of having 3 patients die in the immediate postoperative period of perforated peptic ulcer following the removal of cerebellar tumors during which there had been long-continued use of electrodesiccation. Also, in autopsy material, he had noticed ulceration of the gastric mucosa in 2 cases of cerebral tumors in other locations. There were 2 cases of malignant hypertension which had gastric ulceration, in 1 of which death was due to perforation of the ulcer. He reported a case of duodenal ulcer in a 9 year old female child who had had a cerebral tumor removed and subsequent deep Roentgen ray therapy. One amazing instance was that of a patient with symptoms of cerebellar tumor who was treated by deep Roentgen ray therapy with relief of symptoms. He returned later with recurrence of cerebellar symptoms and duodenal ulcer. On resuming Roentgen ray therapy, the symptoms of both lesions disappeared. This entire sequence of events was repeated again when the patient for a second

time was admitted with symptoms of both lesions.

Very recently Strassman<sup>61</sup> studied the relation of acute mucosal hemorrhages and ulcers of the gastro-intestinal tract to intracranial lesions in a large number of autopsies. He reports that in 26 cases of acute hemorrhagic ulcerations and 30 cases of softenings and perforation of the esophagus, stomach and duodenum, all but 2 were associated with intracranial lesions..

In 1942, Wolf and Wolff<sup>72</sup> studied a patient with a chronic gastric fistula and observed that in situations involving anxiety, hostility and resentment there was a "profound and prolonged hyperemia, hypermotility and hypersecretion."

Thornton, Storer and Dragstedt<sup>63</sup> studied the night secretion of several groups of patients with the following results:

No. cases	Type of case	Average 12 hour night secretion, cc.	Free acidity in clinical units
9	Carcinoma of stomach	261	0-21
5	Carcinoma of colon	238	0-18
6	Gall bladder disease	385	0-13
10	Peptic ulcer	821	47*

\* Average clinical units.

In the duodenal ulcer group, the values after vagotomy dropped to an average night secretion of 385 cc. with free acid values of 0 to 13 clinical units. They regard these as truly impressive data and feel that since the patients were asleep and therefore not subject to stimulation by food or psychic factors, the night volume must be due to abnormally great secretory tonus in the vagus nerves.

Dragstedt and his associates have shown that the stimulation of gastric secretion by insulin hypoglycemia, as described by Hollander,<sup>33</sup> dependent as it is upon central nervous system stimulation, is abolished by vagotomy. They studied, during sleep, gastric tonicity and hunger contractions of the stomach by means of a balloon attached to a Miller-Abbott tube; and, while there is increased tonus and increased frequency and amplitude of hunger contractions in peptic ulcer, there was a definite decrease following vagotomy.

They have shown that caffeine and histamine stimulation, acting on the peripheral neuroglandular mechanism of the stomach, have a pharmacologic action not altered by vagotomy.

Moore, Chapman, Schulz and Jones<sup>50</sup> make the point that the efficacy of atropine in the treatment of peptic ulcer has been due to the fact that it alters the permeability of the cell to acetylcholine, thus blocking parasympathetic impulses at the end-organ. With bilateral vagotomy, then, one has a complete and permanent atropinization of the area. They showed with barium an increase in initial emptying time of the stomach of from 1½ to 15 to 20 minutes; and an increase in complete emptying time of the stomach of from 2 to 2½ to 12 to 24 hours. They showed a lessening of peristaltic activity and of

large gastric contractions, but no change in gall bladder emptying time. They studied sensation in the lower esophagus and stomach to balloon distention but found no change. Dragstedt<sup>15</sup> has, shortly after vagotomy and while the patient feels entirely well, surreptitiously introduced weak solutions of hydrochloric acid into the stomach and reproduced ulcer pain. These 2 facts indicate that sensory fibers to the stomach do not travel in the vagi.

An interesting experience of Moore<sup>49</sup> was reported in 1946. He did vagotomy on a patient who had had a gastric resection without removal of the antrum. Following vagotomy, the patient was not clinically well, but became so when his side-tracked antrum was later removed. This is significant in that it tends to confirm Edkin's<sup>18</sup> work on gastric hormone and the considerable clinical experience with recurrent difficulties when the antrum is retained. According to Babkin<sup>2</sup> there

is a triple mechanism for gastric secretion. The first chemical, induced by such substances as histamine and alcohol; a second hormonal, and a third or psychic one which is the only mechanism interfered with by vagotomy. The symptom complex of peptic ulcer following section of both vagi may be explained on either a chemical or hormonal basis.

Dragstedt<sup>15</sup> has pointed out that Carlson has proved a continuous basal secretion of gastric juice. This basal secretion is augmented by the taste, sight and odor of food. Section of the vagus nerves does not entirely eliminate gastric secretion as this can still be stimulated by the presence of food within the stomach and the liberation of gastric hormone; also, the chemical phase of gastric secretion is not altered as histamine and caffeine act independently of the nerve mechanism.

There is a wealth of experimental work in support of the rôle of the vagus nerve in peptic ulcer. Schiff,<sup>67</sup> in 1867, Brown-Sequard,<sup>9</sup> in 1875, and Ebstein,<sup>17</sup> in 1874, have shown ulceration of gastric or duodenal mucosa to follow central nervous system stimulation by either cauterization or chromic acid injection. von Preuschen<sup>66</sup> and Pomorski<sup>54</sup> confirmed these findings. Mogilnitzky,<sup>48</sup> in 1925, and Burdenko,<sup>10</sup> in 1926, have shown the production of chronic ulceration of gastric or duodenal mucosa due to central nervous system stimulation, and this work has been confirmed by Keller<sup>35</sup> in this country.

Westphal,<sup>69</sup> in 1926, produced ulcers in cats, rabbits, dogs and guinea pigs by the subcutaneous injection of pilocarpine. Light, Bishop and Kendall<sup>43</sup> have shown that very small amounts of pituitrin or pilocarpine injected intraventricularly will produce ulcers of the stomach and duodenum. Beattie<sup>3</sup> has shown that electrical stimulation of the central nervous system will produce vagal stimulation and ulceration of the mucosa of the stomach or duodenum which will be abolished by vagal section. Keppich,<sup>7</sup> in 1921, and Stahnke,<sup>59</sup> in 1924, reported the production of typical peptic ulceration by continuous electrical

stimulation of the vagus nerves. There was hypermotility, hypersecretion and ultimate erosion of the mucous membrane.

The vagal nerve supply to the stomach has been bilaterally sectioned in animals by many workers. Donati,<sup>14</sup> in 1904, sectioned both vagi and reported no ulceration of the mucosa. This was repeated by Lichtenbelt<sup>42</sup> in 1912, Greggio<sup>27</sup> in 1917 and Koennecke<sup>37</sup> in 1922. Beazell and Ivy,<sup>5</sup> in 1936, used bilateral vagal section in rabbits to study the effect of trauma in ulcer production since vagotomy produces stasis. In 1915 Chiari<sup>11</sup> produced chemical block of the vagi with atropine and reported diminished gastric secretion and marked suppression of hydrochloric acid secretion.

From 1919 to 1922, Latarjet<sup>40</sup> did experimental work on animals in which he denervated the stomach of its vagal filaments and found that there were no harmful effects on the animals and that gastric motility was still present. There was, however, definite hypotonicity, delay in emptying and dilatation. He found that for 3 years this state of affairs continued. He noted that such a dog (post-vagotomy) required 7 hours to empty his stomach, whereas only 2 were required before. In this animal, there was also diminished hydrochloric acid secretion and no trophic lesions.

In 1929, Hartzell<sup>30</sup> sectioned the vagus nerve in dogs both intra-abdominally and transthoracically. He found a marked reduction in both the free and total acid, and noted that incomplete section of the vagus nerves caused little or no postoperative secretory change. Vanzant,<sup>64</sup> in 1932, reported further studies on these same dogs. Their gastric acidity had returned to normal and reexamination of the operative sites in 3 dogs showed that the nerves had not regenerated. There was still a slight delay in emptying and a slightly subnormal response to histamine. Pieri and Lapenna<sup>52</sup> showed the same changes in the human being.

In 1931, Beaver and Mann,<sup>4</sup> working with the Mann-Williamson preparation in

dogs reported failure of the usual peptic ulcer formation when vagotomy was done. The rate of occurrence in a sympathectomized group was the same as in the control group.

Shapiro and Berg,<sup>58</sup> in 1932, created Pavlov pouches and did gastrojejunostomies in a series of dogs. Before vagotomy the acid in the pouch showed 100 to 120 clinical units, and after vagotomy only 40 to 50. The main gastric values ranged from 85 to 100 clinical units and fell to 40 to 50 units after vagotomy. There was also marked skin irritation around the pouch opening before vagotomy, which cleared after vagotomy. In 4 to 5 weeks, however, the acid values returned to normal and the skin irritation from the pouch discharge returned.

One may say now that for those cases of peptic ulcer in which the psychic phase of gastric secretion is greatly increased (due to central nervous system disturbance brought to bear on the gastric glands through the intermediary of the vagus nerve) section of the vagi is rational. Hyperemia of the mucosa seems to be associated with hypersecretion. There is evidence, both clinical and experimental, that section of the vagi at the esophageal plexus and distally does no harm, within short subsequent periods of time at least; but there is considerable evidence that the resulting hypoacidity and hypomotility may not be permanent.

Fulton,<sup>22</sup> in his discussion of the vagus nerve, describes the synaptic junctions in the wall of the stomach in the ganglia of the myenteric and submucosal plexuses. He states that the parasympathetic activity promotes digestion and aids in the passage of food through the gut. When stimulated, peristalsis is increased, the sphincters relaxed, and the production of gastric juices including salivary and pancreatic are stimulated. Digestion, however, can proceed adequately following bilateral section of the vagi at the level of the diaphragm, and bilateral section of the splanchnic nerves. The preoperative

level of tonus and peristaltic activity is soon reestablished.

The anatomy of the vagus nerves is not so well established. According to Gray,<sup>26</sup> the vagus nerve, which has the most extensive course and distribution of any of the cranial nerves, contains somatic, motor and sensory fibers and parasympathetic efferent fibers. On the distal end of the esophagus, the vagi form a plexus, tend to reform into 2 main trunks and, passing through the diaphragm, break up into small filaments along the lesser curvature. We may schematically represent this as in Figure 1.<sup>23</sup> It is the parasympathetic efferent fibers, arising from the dorsal nucleus of the vagus, which principally concern us. These are preganglionic fibers to the thoracic and abdominal viscera. They end in small ganglia in or near the organ and postganglionic fibers carry the impulse to the end-organ. In the abdomen, the effects of the parasympathetic fibers to the stomach and small intestine are augmentory; the sympathetic inhibitory. The removal of the effects of 1 set of fibers, as by section, results as a rule in the effects of the other set seeming more prominent. This indicates that each type of fiber exerts a constant or tonic action and suggests that the 2 effects are delicately balanced one against the other.

Walters, Bradley, Small and Wilson<sup>68</sup> made dissections in more than 100 autopsy cases. They found that while the vagi do, in varying patterns, tend to form 2 main trunks on the lower esophagus, in 8% of the cases the fibers took such a course that it would have been very difficult to completely section them below the diaphragm. Miller and Davis<sup>46</sup> studied the vagus nerves in autopsy specimens and concluded that the variations in the course of the fibers are such that section should be done transthoracically.

Jackson<sup>34</sup> in a study of the vagus in 26 cadavers showed the varied courses of the vagus both on the lower esophagus and on the stomach itself. He also reports a clinical application of this knowledge in that the branch from the posterior vagus

which goes to the celiac plexus may be preserved by leaving the main trunk and the celiac division intact and dividing the remaining segments of the gastric branches of the posterior nerve alone. This he calls "selective vagal resection." Dragstedt<sup>15</sup> has noted fibers traveling in the wall of the esophagus itself.

Since 1943, when Dragstedt<sup>15</sup> first reported on this procedure, the clinical literature on vagotomy is fast growing. His performance of this operation was preceded by many years of work on gastric physiology and in his reports on this procedure he has at some length given his reasons for considering this a rational

### FUNCTIONAL COMPONENTS OF THE VAGUS NERVE (GARDNER)

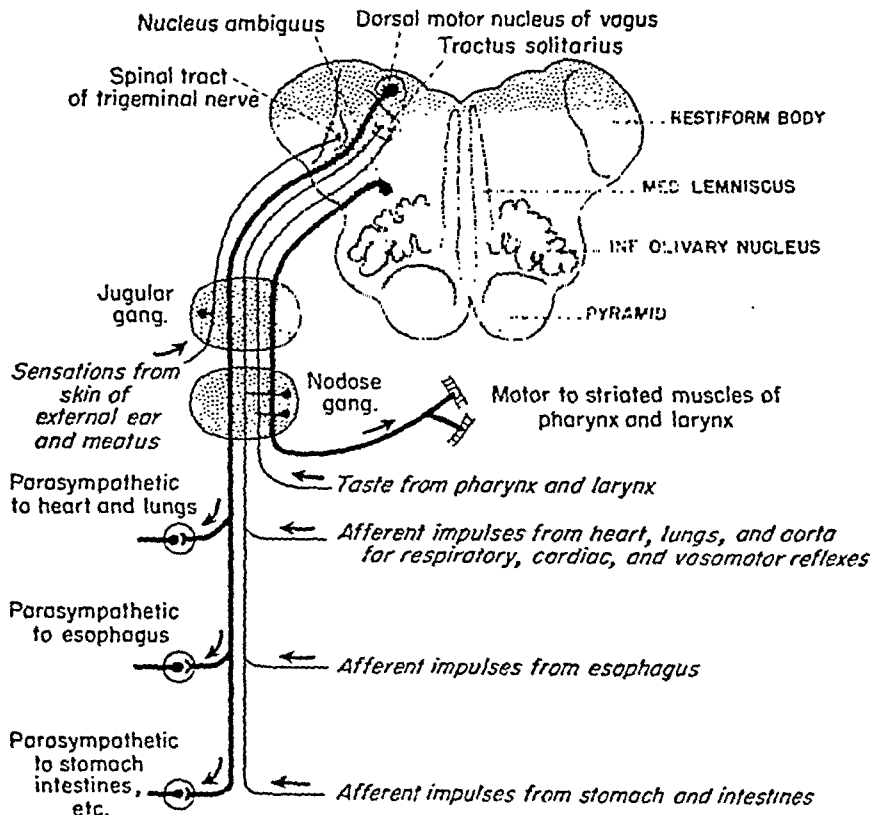


FIG. 1.—Functional components of the vagus nerve.

We are now in the process of studying the exact degree of variation of the course of the vagus through the posterior mediastinum and shall report on this later. In the operation of vagotomy, an attempt is made to section completely nerves, the anatomy of which is not constant, and in so doing we of necessity disturb an existing delicate balance of nervous control of the gastro-intestinal tract by the sympathetic and parasympathetic nervous system.

procedure. His first 40 cases were done by the transthoracic route which he abandoned because of complaint of pain along the course of the affected intercostal nerve. This we have noted in our series and shall comment on it later. Moore, Chapman, Schulz and Jones<sup>59</sup> have also reported on 50 cases done by the transthoracic route. Grimson *et al.*<sup>23</sup> have reported on 40 cases done transthoracically.

Our first 15 cases were done transthorac-

ically for the following reasons. The procedure was suggested only in proven cases of duodenal ulcer or post-gastrectomy complications in which we felt nothing would be gained by seeing the lesions. All had the typical peptic ulcer syndrome with definite Roentgen ray findings and high free acid so that we felt the diagnosis was well established. They represented medical failures or surgical failures in both coöperative and uncoöperative patients. Further, we not only felt that complete resection of the vagus nerve could be more easily accomplished transthoracically, but we were interested in the appraisal of vagotomy alone as a method of treatment, and felt that appraisal of its efficiency when combined with gastro-enterostomy might be misleading.

The advantages of transthoracic vagotomy are the ease with which the vagus can be sectioned and the fact that it may be employed shortly after acute perforation. We feel that complete section, which is important, is more nearly possible in every case by this route. The disadvantage is that the lesion is not seen unless one opens the diaphragm, which we have not done, but which has been done by Moore<sup>50</sup> routinely in at least his first 12 cases. It offers decided disadvantages if it is advisable to see or feel the lesion and would not be employed by choice if one were confronted with the necessity of also doing gastro-enterostomy for obstruction. We have, however, used transthoracic vagotomy only for those cases of peptic ulcer in which the diagnosis had been established by repeated Roentgen ray examination and substantiated by incidents of previous hemorrhage, perforation or obstruction. In most cases we felt we would learn no more about the patient by examination of the ulcer *in situ*.

In our hands section of the vagus is easier transthoracically and offers better opportunity for complete section, and we reserve the abdominal route for those unusual cases in which there is question of obstruction or associated pathology.

Dragstedt has reported on another 100

cases done by the transabdominal route, and Walters *et al.*<sup>68</sup> also have reported on large series of cases done by the subdiaphragmatic approach. Crile<sup>12</sup> has recently reported 77 cases done by the subdiaphragmatic route. Undoubtedly there will in a few more years be reports of much larger series done by both methods and with longer periods of postoperative observation.

We have done abdominal vagotomy in 7 cases. Four gastro-enterostomies were done in these cases, but in retrospect we think 2 were not necessary.

The indications as described for vagotomy are similar in all recent reports. It is being done primarily for duodenal ulcer for which medical management has failed, so that the patient either continues to have his symptom complex or during course of active treatment has developed such complications as hemorrhage, obstruction or perforation. Secondly, it is being done for surgical failures such as jejunal ulcer following either gastro-enterostomy or gastric resection. A few cases of vagotomy have been reported for gastric ulcer, but these have been done for very particular reasons. Of our 32 cases the ulcer was duodenal in 27 cases, gastric in 2 cases, jejunal in 4 cases and 1 case had gastro-jejunocolic fistula. The duration of the peptic ulcer syndrome in these cases varied from 1 month to 24 years, and the average was 8 years. The 2 cases of gastric ulcer were admitted to the hospital for acute perforation, which at time of gastrorrhaphy presented no unusual findings and had pathologic confirmation of ulcer by biopsy. Their transthoracic vagotomies were done 9 and 17 days following the gastrorrhaphies. These cases were done too recently for comment, but they are being followed very closely. We feel that 1 perforation of duodenal ulcer is sufficient reason for vagotomy and where there is no obstruction following simple repair, we proceed during the next week or 2 to do a transthoracic vagotomy and then discharge the patient to the follow-up clinic.



It was necessary in all cases to treat postoperative gastric atony rather vigorously, but in only 1 case did we feel gastro-enterostomy might be advisable, and that patient refused operation. In all cases we have kept the patients on intermittent gastric suction for from 2 to 10 days; intermittent, as we at the same time insisted upon early ambulation. We have used tetra-ethyl ammonium bromide in 2 cases. This should relax the pyloric sphincter if the obstruction is due to an imbalance of nervous control. We felt that the drug was of benefit in 1 case. In the second case, we could see no effect on the pylorus under fluoroscopy and discontinued the drug.

It has seemed strange to us that other chest procedures in which thoracotomy incisions are used cause so very much less intercostal pain than does vagotomy; and this fact must be related to the nervous disposition of the ulcer patient. We have had less complaint than has been reported in other series, possibly due to our extensive use of intercostal block, but it can always be elicited by question. In our later cases we have either crushed or sectioned the intercostal nerve and feel that this is a good procedure.

We have also employed intercostal block on the left from the sixth to the tenth ribs very freely, using about 5 cm. of 1% novocaine to each nerve, and repeating the injection as symptoms dictated, sometimes as often as every 5 hours for 2 to 5 days. Such nerve blocks allow earlier return to full function of the left chest.

The 1 case which we felt had become obstructed left the hospital on the 5th postoperative day and was not seen again for 8 weeks. We feel that his obstruction was organic only on the basis of long-continued gastric dilatation and that this could have been prevented by closer observation and decompression. We very seriously doubt the necessity for subjecting the patient to the added hazard of gastro-enterostomy in any case which does not have pre-vagotomy obstruction. Several of our cases have had Roentgen ray

diagnosis of grossly deformed duodenal bulbs, but still have had no more than ordinary postoperative difficulty.

Very little mention has been made in the recent literature concerning anesthesia for vagotomy. Transthoracic section should not be attempted without excellent anesthetic supervision. With proper anesthesia the operation is technically easier to perform transthoracically than abdominally. We have had no fear of vago-vagal reflex since our Anesthesia Staff feels that it seldom, if ever, happens under ether anesthesia.<sup>62</sup> We have used no precautions concerning injection of the nerve before section; nor have we transplanted and fixed the proximal end to the pleura after section as Moore and Dragstedt have done; nor have we attempted to repleuralize the esophageal bed. This simplifies the operation to the point where one may expose through the left pleural sac from 2 to 4 inches of the esophagus under controlled respiration anesthesia (using ether as the anesthetic agent), and locate the vagus nerves and the lower portion of the esophageal plexus in order to do a complete section.

Complete resection of both vagi is the essential of the operation. The gastric secretory glands must be made inaccessible to central nervous system influences. Hartzell<sup>30</sup> has shown the necessity for this by pointing out that partial section does not give quantitative reduction of acid secretion. Vanzant<sup>64</sup> has shown return to normal acid secretion in dogs 2 years after section. Shapiro and Berg<sup>53</sup> show an even more rapid return to normal in their animals. Pieri<sup>65</sup> has reported in his patients, in some of whom he had sectioned only the left vagus, that "following the operation there was a lowering of the hydrochloric acid and of pepsin, a lowering more conspicuous in the cases in which the section was bilateral, but that postoperatively the hydrochloric acid and pepsin rose progressively and in some cases reached or surpassed the preoperative figures." He thought this was to be understood on the basis of "the mechanism of functional

compensation, obscure but sure, that takes place in the vegetative nervous system." Our series of cases is neither great enough nor the follow-up studies long enough for us to offer information on these points.

White and Smithwick,<sup>70</sup> commenting on this, think that the return of function could be due to (1) the high degree of automaticity of the digestive process so that it can be regulated by the intramural plexus, (2) the presence of mixed components of the splanchnic and vagal trunks, or (3) the fact that preganglionic fibers have such an extraordinary power of

lishment as a worthwhile therapy on the European continent, we feel that return of some acid secretion post-vagotomy on the basis of automaticity was not the factor, but incomplete section of the nerves instead. We have reproduced a chart from McCrae's<sup>45</sup> article in 1925 which roughly illustrates their operative attack upon the vagi (Fig. 2). Incomplete section is most likely to happen in the Latarjet procedure, less likely in the Exner or Dragstedt procedures where the lower esophagus is well mobilized from below, but we feel least likely to happen when 3 or 4 inches of the

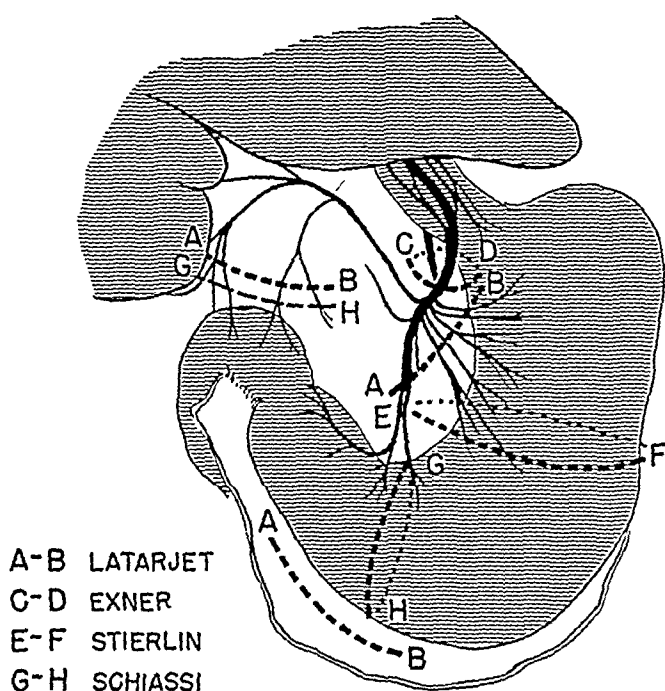


FIG. 2.—Diagram illustrating earlier operative methods of performing vagotomy.

regeneration. The second point does not explain failure of ulcer formation in peripheral stimulation of the sympathetic nor the sharp contrast in results using the Mann-Williamson preparation in dogs with and without sympathetic and vagal section. The third has been disproven by both Vanzant<sup>64</sup> and Dragstedt.<sup>15</sup> The latter claims that the vagal trunks do not regenerate even when immediately resutured. The automaticity characteristic must explain the return of acid production to normal.

If vagotomy failed of successful estab-

ishment as a worthwhile therapy on the European continent, we feel that return of some acid secretion post-vagotomy on the basis of automaticity was not the factor, but incomplete section of the nerves instead. We have reproduced a chart from McCrae's<sup>45</sup> article in 1925 which roughly illustrates their operative attack upon the vagi (Fig. 2). Incomplete section is most likely to happen in the Latarjet procedure, less likely in the Exner or Dragstedt procedures where the lower esophagus is well mobilized from below, but we feel least likely to happen when 3 or 4 inches of the

this reason, but feel that, if after 6 to 12 months our patients should begin having chronic dyspepsia, the test would then apply.

We have also used the night secretion test of Dragstedt<sup>15</sup> as a test of hypertonicity of the vagus. The test is open to 2 inaccuracies in that an uncoöperative patient may drink fluids or any patient may lose fluid through the pylorus. The test gives quite variable results if used in patients who have had gastro-enterostomy or resection. We have also noted that following vagotomy one may obtain a high night secretion (in 1 case 1200 cc.) and that one may also obtain free HCl readings of as high as 40° and still have a negative hypoglycemic reaction. This we must explain on the basis of Babkin's<sup>2</sup> theory of the triple phase of gastric secretion only one of which is interfered with by vagotomy. It is then possible to have high acid secretion still on either the basis of chemical or hormonal stimulation.

It is because of such discrepancies and the fact that the operation was once discontinued that we feel such cautions as those of Lahey<sup>33</sup> apply. He compares our present-day enthusiasm for vagotomy with that once mistakenly exhibited for gastro-enterostomy and total thyroidectomy. He prefers vagotomy now for those cases in which gastro-enterostomy will not be necessary and for postsurgical complications, and in conjunction with subtotal gastrectomy for duodenal ulcer.

We have had 1 recurrence of ulcer following vagotomy. This patient had duodenal ulcer for 10 years and was seen in the sanatorium where he was being treated for advanced bilateral pulmonary tuberculosis. Only 1 routine gastric analysis was done preoperatively and that showed high free HCl acid. A transthoracic vagotomy was done following which, despite some difficulty with gastric atony, he was symptomatically well for 16 days. He then had a recurrence of typical chronic dyspepsia with epigastric pain which continued in varying severity for several months. Finally there was an attack of

very severe epigastric pain and some degree of vascular collapse, and he expired 48 hours later. Autopsy showed an ulcer on the lesser curvature bordering on the esophago-gastric junction with perforation and generalized peritonitis. The duodenal ulcer was present but appeared inactive. It measured 3 cm. in greatest diameter, while the gastric ulcer was 2 cm. in diameter. Unfortunately there was such tissue destruction from infection and postmortem autolysis that examination of the lower esophagus for incomplete section of the vagi was unsatisfactory. Since the surgeon felt he had done complete section, one can only speculate on such factors as intramural fibers of the vagus or gastric ulcer on some basis other than neurogenic such as hormonal or chemical or histamine absorption from pulmonary tissue destruction.

Almost uniformly, however, our patients following this operation claim they are well. Their peptic ulcer symptom complex with which they were so familiar disappeared, and none of them confused his difficulties of gastric atony with his preoperative disease. They have gained weight on unrestricted diet and have in some cases resumed smoking and drinking—pleasures which had previously been denied them.

Moore,<sup>51</sup> in his recent edition of "Modern Treatment of Syphilis," says of this operation for gastric crisis in *tabes dorsalis* that more experience is "urgently desirable." We feel that the same may be said of peptic ulcer of the duodenum and for postgastrectomy complications of peptic ulcer with the possible exception of those few cases in which there is retained antrum.

The experience with resection of the vagus nerve in the treatment of duodenal ulcer appears very heartening indeed. However, it is of importance to point out that except for the frequent sporadic use of this procedure in the past, the operation has actually been performed only over the past 4 years. When one remembers the glowing reports from the use of gastro-

enterostomy for the treatment of duodenal ulcer, our inclination is to be cautious about final results. At this stage it is impossible to state what the status of vagotomy will be 10 years from now. The results so far in our clinic have been impressive. If the procedure provides even temporary help to those individuals who have developed jejunal ulcers after what appears to have been an adequate gastrectomy, the operation will be a decided ad-

vance providing no serious permanent sequelæ result from the operation. We have noted nothing which would indicate that serious sequelæ result. It has been well emphasized in many of the articles on vagotomy that this procedure should be carried out only after a very careful evaluation of the patient and the patient who had a vagotomy should have a very careful follow-up for evaluation of results.

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## OPHTHALMOLOGY

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## OCULAR LESIONS IN BRUCELLOSIS

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DETERMINATION of the etiology of iritis, uveitis and choroiditis, especially of the chronic or recurrent type, is an almost daily problem which confronts the ophthalmologist and his consultants. The clinical appearance of some of the lesions is sufficiently characteristic to warrant a presumptive diagnosis of the cause. In many instances, however, the lesions are of non-specific type and clues to the etiology must be sought through the history of the patient, systemic examination and laboratory tests. And even if the clinical appearance is suggestive of a certain etiology, confirmatory findings are desirable before a definite diagnosis is established. Unless extensive studies are carried out, which may at times seem almost too exhaustive, the cause of many cases will go undetermined. Examinations carried out by Woods and Guyton<sup>15</sup> included general physical examination, laboratory examinations of urine, hemocytology and blood chemistry, serologic tests for syphilis, intracutaneous tests for tuberculin sensitivity, roentgenologic examination of the chest, search for foci of infection, gonococcus complement fixation tests, agglutination tests for brucellosis, biopsies of lymph glands, estimation of serum albumin and globulin, roentgenograms of the hands and feet, special bacteriologic examinations, sensitivity studies, examination of spinal fluid and neutralization tests for toxoplasma, and yet the cause remained undetermined in 22 of 200 cases.

Twenty-five or 30 years ago, focal infection was quite generally accepted as the cause of those lesions of the uveal tract which could not be assigned definitely to syphilis, tuberculosis or bacterial metastasis in the course of an active infection. Even in the 1941 series of Guyton and Woods,<sup>8</sup> in which more complete studies were carried out, the cause was stated to be either syphilis, tuberculosis or focal infection in 86% of 562 cases. In the 1943 series of Woods and Guyton,<sup>15</sup> this percentage had dropped to 61. The percentage of cases assigned to focal infection had dropped from 26 in the 1941 series to 6 in the 1943 series. In the 1943 series, 7.5% were attributed to sarcoidosis and 7.5% to brucellosis as against 0.5% and 0.4% in the 1941 series.

It is well known that metastatic involvement of the uveal tract can occur in the course of streptococcic, staphylococcic, pneumococcic, meningococcic and other septicemias. It would be logical to assume that similar inflammations of the eye might occur in acute cases of Brucellosis when the organisms are present in the blood stream. This assumption seems to be supported by experimental and clinical evidence. Fabry<sup>5</sup> stated, in 1912, that, following intra-abdominal or subcutaneous inoculations, *Bacillus abortus* caused lesions in guinea pigs of a practically constant and most remarkable character. The acute changes appeared usually between the 3rd and 6th week

after inoculation and continued over a period of 10 to 20 weeks accompanied by fever. The disease tended to final recovery; but the animal might die from rupture of the spleen or as the result of emaciation and exhaustion. Three of his animals developed blindness in 1 or both eyes as the result of opacity of the cornea. Histologically, the sclera, choroid and lacrimal glands of the diseased eyes showed areas of infiltration, chiefly of lymphoid elements. Some typical tubercles were seen and also intracellular bacilli. Orloff,<sup>12</sup> in 1928, reported on the histologic examination of the eyes of 19 guinea pigs that developed lesions of the cornea and lens during the course of Malta fever. These animals were among a group of 200 affected in an epidemic. The eyes showed circumcorneal injection, clouding of the cornea, either centrally or in the form of a gray infiltrate fading out from the margin to the center, hyperemia of the iris with posterior synechiae or with the pupil filled with grayish exudate. Histologically, the changes in the cornea varied from mild cellular infiltration with degeneration of the epithelium and endothelium to thick cellular infiltration with formation of new vessels resembling the lesions of syphilitic parenchymatous keratitis. Diffuse and focal infiltration with lymphoid and epithelioid cells and endovasculitis and perivasculitis was found in the iris, the ciliary body and the anterior part of the choroid. These changes were most definite and extensive in the ciliary body. In the retina, degeneration of the ganglion cells and edema of the outer nuclear layer and of the layer of rods and cones were noted. Orloff thought that the lesions were produced partly through the action of toxins and partly by direct invasion by the organisms. In 1939, Burky, Thompson and Zepp<sup>4</sup> presented strong evidence that infection with *Brucella abortus* is a cause of periodic ophthalmia in horses which is similar to recurrent endogenous uveitis in humans. In the course of their experiments, they demonstrated that 1 of the strains of brucella that they had re-

covered would, on intravenous injection into rabbits or on direct inoculation into the eye, produce a generalized kerato-uveitis similar clinically to severe tuberculous lesions and resembling histologically periodic ophthalmia in horses and chronic recurrent intraocular inflammation in humans.

Most of the reports of ocular lesions occurring in association with brucellosis have dealt with cases in the acute phase of the disease. Thus, in 1939, Green<sup>6</sup> collected the reports of 23 authors (cases of Aurand, Aubaret and Roger, Villard and Pech, Bergmark, Bingel and Jacobstiel, Cannavo, Cohen Boulakia, Godwin, Lemaire, Lundsgaard, Levy and Uzan, Aubaret and Guillot, Madievskaya, Roger, Villard and Viallefont and Temple, Rizzo, Mossa, DeJong, McCullagh and Clodfelter, Rutherford, Carranza, Roger, and Sella). In all the cases, the brucellosis was in an acute or at most in a subacute phase. The optic nerves were involved in 14 cases, in the form of optic neuritis in 9, in the form of choked disk in 4, and in 1 of Rutherford's cases, possibly as the result of subarachnoid hemorrhage rather than of the brucella infection itself. Meningitis was stated to be present in 4 of the cases with optic neuritis and in all of the cases with choked disks. Paralysis of ocular muscles were described in 6 instances, all with meningitis. Involvement of the uveal tract was reported in 7 cases and of the retina in 1 case. Brucella organisms were cultured from the blood in 3 of the cases with uveitis and in the case with septic retinitis. In the discussion of Green's paper, Snell<sup>14</sup> reported a case of central retinitis and Blake<sup>3</sup> the recurrence of a dendritic ulcer of the cornea, which occurred in each instance during the active stage of brucellosis. A study of these reports still leaves open the question whether iritis, uveitis or choroiditis can develop as the result of brucellosis in its chronic or latent phase.

Green<sup>6</sup> reported at the same time 4 original cases. In 2 of these, the brucella infection was in an acute phase apparently.

One of these patients had central retino-choroiditis and the other optic neuritis. A third patient had, during the chronic or latent stage of brucellosis, recurrences of a phlyctenular keratoconjunctivitis, the first attack of which had occurred during the acute stage of the infection. In the fourth patient, who had active central choroiditis, there was no history of an acute illness and the diagnosis was based on a strongly positive reaction to a cutaneous test for *Brucella abortus*. In 1943, Green<sup>7</sup> presented a case of chronic progressive kerato-iritis which he believed to be due to chronic brucellosis. It was his opinion that adequate laboratory tests for brucellosis should be made routinely in every chronic inflammatory lesion of the uveal tract and that, if the diagnosis were established, prompt energetic treatment with a brucella vaccine might check the progress of the disease. Berens,<sup>2</sup> on the other hand, was inclined to think that ocular brucellosis must be quite rare. He stated that skin tests with *Brucella abortus* antigen were made on 39 patients with inflammatory lesions of the eye, mainly involvements of the uveal tract. A positive reaction was obtained in only 1 patient with uveitis. Agglutination tests for *Brucella abortus* were done on 43 patients and for *Brucella melitensis* on 5 patients. All were negative.

Reed and Goldfain<sup>13</sup> stated that ocular symptoms and signs may occur in an individual with chronic brucellosis. They reported 3 cases of recurrent iritis in all of which the skin tests were positive and agglutination tests were positive in dilutions of 1:200. They included in their report also a case of recurrent ulcer of the cornea in which the skin test was positive but the agglutination negative.

Harris<sup>9</sup> reported 3 cases of recurrent iritis and 1 case of recurrent keratitis which he attributed to brucellosis. One of the patients with iritis had run a low grade fever for 5 years. An agglutination test was negative, but the cutaneous reaction was positive and the phagocytic index was low. Later, this patient developed men-

ingo-encephalitis and died. *Brucella* had been isolated from the stool of another patient with iritis 1 year before observation. At the time of observation, an agglutination test was negative but an intradermal test with brucella antigen was strongly positive and focal reactions occurred in the choroid after the intradermal test and after the subcutaneous injection of 0.1 cc. of mixed brucella filtrate. A woman had had recurrent keratoconjunctivitis for 4 years. An agglutination test was negative, but the cutaneous reaction was positive and the phagocytic index was low. Clinical recovery was complete after 4 months treatment with *Brucella abortus* vaccine. The phagocytic index was high and there was no recurrence during an 18 month period of observation. In a case of uveitis reported by Agin,<sup>1</sup> the diagnosis of brucellosis was based on a strongly positive skin test. In spite of vaccine therapy, the uveitis terminated in phthisis bulbi. The eye was enucleated, but the results of histologic examination were not available at the time of the report.

Jones and Norris<sup>10</sup> reported 1 case of acute uveitis and 1 of conjunctivitis occurring in individuals who had positive skin tests for brucellosis. They mentioned also some interesting observations, the interpretation of which is not quite clear. They mapped the tangent screen fields of 111 persons some of whom had visual complaints, some of whom had only physical complaints, and some of whom were included in a routine study of individuals who came in contact with certain chemicals. Ninety-two (81.4%) of these individuals showed widening of the normal angioscotomas (Evans). Of the 92, 75 (81.5%) gave positive skin reactions indicative of brucellosis. Of 19 persons in whom the angioscotomas were of normal width, only 3 (15.7%) gave similar positive skin reactions.

In their paper on "The Rôle of Sarcoid and of Brucellosis in Uveitis," Woods and Guyton<sup>15</sup> present an analysis and evaluation of 15 cases which they attributed to



brucellosis. Seven of the patients had recurrent iritis; 5 had generalized uveitis; 3 had only lesions in the choroid, "1 or more elevated moderately circumscribed exudates with little surrounding reaction or generalized subretinal edema." The uveitis was of granulomatous type in 8 cases and of non-granulomatous type in 7. It was recurrent in 11 of the 15 cases. The cornea was involved in 2 cases. An additional case of nummular keratitis is mentioned as occurring in a patient with chronic brucellosis and the question is raised as to the possible etiologic rôle of brucellosis in nummular keratitis. One case of uveitis progressed to phthisis bulbi and the eye was enucleated. Histologic examination revealed "a non-specific uveitis with several conspicuous lymphoid nodules, a picture quite suggestive of that of periodic ophthalmia in horses." All of the patients gave a history of ingestion of raw milk or raw milk products and most of them had had unexplained fever previously. Only 1 patient had a prolonged low grade fever during the period of observation. Hence the patients must have been in the chronic or healed phase of the infection. Agglutination tests against *Brucella suis* and *Brucella abortus* antigens of living organisms were positive in dilutions of 1:20 to 1:320 in 13 of the 15 cases. In 1 patient, agglutination tests were negative but the complement fixation reaction was strongly positive. In the remaining patient, both the agglutination and the complement fixation tests were negative, but "the cutaneous sensitivity test was violently positive and there were no other etiologic factors." A cutaneous sensitivity test was done on only 5 patients; it was positive in 4 and negative in 1.

It is generally recognized that it is very difficult to establish a positive diagnosis of chronic brucellosis. In most instances, the diagnosis must be taken to be presumptive only. The brucella organisms cannot be cultured from the blood in chronic cases. The agglutination titer is high in the acute stage but drops as the

case becomes chronic and may even fall to zero while the patient still has a low grade fever. The complement fixation reaction is not thought to be satisfactory for diagnostic purposes because it is not sufficiently specific. Woods and Guyton<sup>15</sup> checked the complement fixation reactions of 76 patients for both brucella and gonococci; 21 patients were positive to brucella but 18 of the 21 were positive to gonococci also. Woods and Guyton<sup>15</sup> seem to favor the employment of agglutination tests for diagnostic purposes and do not place much reliance on the cutaneous sensitivity tests or the opsonocytophagic index. However, Green,<sup>7</sup> Harris,<sup>9</sup> and McGinty and Gambrell<sup>11</sup> seem to favor the combined appraisal of the cutaneous sensitivity test and the opsonocytophagic index, since they think that the agglutination reaction is apt to be negative in the majority of cases of chronic brucellosis.

Harris<sup>9</sup> thinks that the agglutination test is of diagnostic significance only when it is positive in dilutions of 1:80 or higher. Harris<sup>9</sup> states that the intradermal test for brucellosis is comparable in all respects to the tuberculin test. He agrees with McGinty and Gambrell<sup>11</sup> that a positive reaction indicates only that the patient has been infected at some time and that it gives no information as to the present status of the infection. By determining the phagocytic activity of the leukocytes towards brucella organisms, however, it is possible to determine whether infection is still present or the patient is immune. The skin test may be made with a heat-killed suspension of brucella organisms in saline or with brucellerin, a suspensoid of nucleoprotein from brucella cells. McGinty and Gambrell<sup>11</sup> prefer brucellerin since it is more standardized and causes less systemic reaction and less local necrosis. Also it interferes less with the agglutination and opsonocytophagic tests. Harris<sup>9</sup> prefers the use of 0.1 cc. of a heat-killed vaccine prepared from the abortus strain only. Harris<sup>9</sup> thinks that the opsonocytophagic

test is of value for 2 reasons: (1) to determine the degree of specific resistance of the patient to brucella organisms as an aid to interpretation of the cutaneous reaction; and (2) for comparison with future tests if the patient is given vaccine therapy.

It would appear that the treatment of acute and chronic brucellosis is not entirely standardized or satisfactory. Among methods of treatment are mentioned sulfonamides, artificial fever, intravenous typhoid vaccine, human immune or convalescent serum, antiserum produced by inoculation of animals with live organisms, brucella vaccines and brucellin. For the acute stage, Harris<sup>9</sup> suggests sulfadiazine or sulfathiazole, transfusions of immune or non-immune blood, Foshay's antiserum. He thinks that artificial fever is of value only occasionally. For the treatment of chronic brucellosis, Harris<sup>9</sup> prefers the intramuscular administration of a vaccine made from the abortus strain alone. Among 400 patients so treated, satisfactory results were obtained in 75%, good

results in between 15 and 20%. The treatment failed in about 5 to 10%. He stated that the only commercially available vaccines obtainable at the time his paper was written (1944) were prepared from mixed strains of brucella and might give undue reactions.

Finally, in attempting to evaluate the rôle played by chronic brucellosis in the etiology of acute, chronic and recurrent iritis, choroiditis and uveitis, it would seem to be logical to accept the views of Woods and Guyton.<sup>15</sup> A positive diagnosis cannot be made since it is not possible to isolate the organism and therapy is not sufficiently adequate to constitute a therapeutic test. However, "the accumulated evidence indicates brucellosis is probably an etiologic factor in uveitis, and it may be quite an important one." Positive agglutination and sensitivity reactions to brucella in a patient with uveitis have probably essentially the same significance in the diagnosis of etiology as positive reactions to tuberculin.

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# BOOK REVIEWS AND NOTICES

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**HUMAN EMBRYOLOGY.** By BRADLEY M. PATTEN, Prof. of Anatomy in the Univ. of Michigan Medical School. Pp. 776; 446 ills., 53 in color. Phila.: Blakiston, 1946. Price, \$7.00.

This new volume is an excellent textbook of embryology for the medical student. The author is eminently qualified to write on this subject, being both a teacher of medical students and writer of well-known texts on the embryology of the pig and the chick. In this book he has aimed at presenting only those aspects of this tremendous subject that have a direct bearing on human development, normal or abnormal. The book begins with an introductory chapter on general embryology, its place in science and, in particular, its place in medicine. This is followed by chapters on the reproductive organs and the sexual cycle, followed by the early development of the embryo, the establishment of the organ systems and the general growth and development of the body as a whole. After a chapter on monsters and teratology there are 11 chapters describing the development of each of the organ systems. Each portion is presented so that it emphasizes its relation with the other subjects of the medical curriculum.

The book is well written, the illustrations are excellent and the Bibliography most complete. It is printed on good paper and is well bound. Besides being of great value for students, physicians in all branches will find this book most helpful as a reference text. It can be most highly recommended.

W. S.

**CHARLES - EDUARD BROWN - SEQUARD, a 19TH CENTURY NEUROLOGIST AND ENDOCRINOLOGIST.** By J. M. D. OLMSTED, Ph.D., D.Sc., Prof. of Physiology, Univ. of California. Pp. 253; 2 ills. Balt.: The Johns Hopkins Press, 1946; London: Humphrey Milford Oxford Univ. Press, 1946. Price, \$3.00.

This monograph records the 8th series of Hikojo Noguchi Lectures of the Johns Hopkins Institute of Medicine. The many

references to Brown-Sequard's medical writings, the biographic references and a good Index make this a scholarly source of information about the man and his work.

To this something has been added. The reader will be delighted by an excellent biography. The hero, in spite of some faults, captures one's attention and affection. His time spent in the United States will arouse the interest of American readers. In the last analysis it is Dr. Olmsted's literary skill which makes this a book to read for pleasure, a rare quality in medical writing. F. L.

**SURGICAL PATHOLOGY.** By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P., (LOND.), LL.D., Prof. of Pathology, Univ. of Toronto. 6th ed. Pp. 858; 530 ills., 22 in color. Phila. and London: Saunders, 1947. Price, \$10.00.

This edition remains an outstanding contribution to the field of surgical pathology, and is an excellent source of information to the pathologist and student. Several additions have been made, and newer concepts of pathologic processes are included. Sections on fibrous dysplasia and pinealoma add to the completeness of the book. Recent theories concerning eosinophilic granuloma are considered. The subject of cystosarcoma phalldes is perhaps too rapidly dismissed. There is an interesting new addition of congenital cardiac defects that are amenable to surgical treatment.

I. Z.

**TUBERCULOSIS AS IT COMES AND GOES.** By EDWARD W. HAYES, M.D., A.C.P., Assoc. Prof. of Tuberculosis, College of Medical Evangelists, Los Angeles; Medical Director and Physician-in-Charge of the Maryknoll Sisters Sanatorium, the Keane Sanatorium, and the Lair Sanatorium, Monrovia, Calif. 2nd ed. Pp. 209; 34 figs. Springfield, Ill.: Charles C Thomas, 1947. Price, \$3.75.

This edition of a book written for patients has increased the space devoted to tuberculin testing and case finding, in line with im-

proved methods instituted since the publication of the 1st edition in 1943. In some instances, diagrammatic figures have been added to complete case histories, and other cases have been included. Other additions include the Dock theory on rest, expansion of the chapters on surgery, a brief mention of rehabilitation, and a section on "Suggestions to Visitors," the latter by Laurence de Rycke, Ph.D. Relatively little attention is devoted to drug therapy, and no information is given to orient patients with respect to the newer methods of medical treatment of this disease, which have been widely publicized in recent years. A pleasing format and the increased use of bold-face type to accomplish emphasis add to the attractiveness of the new edition. E. L.

**CIRUGIA OCULAR.** By H. ARRUGA. Pp. 888; 1218 ills., 119 in color. Barcelona and Buenos Aires, Salvat Editores, S. A., 1946. No price given.

THIS is a complete textbook on the surgery of the eye, of over 800 pages, magnificently illustrated. The illustrations are so extraordinarily beautiful that even if one cannot read Spanish, the author's intent is made clear. Since most operative techniques can be made clearer by illustrations than by the written word, the language difficulty should not prevent anyone from buying this book. The author is well recognized in this country as an authority on retinal detachment and because of his many original contributions to all phases of ophthalmic surgery. He and the publishers are to be congratulated on this magnificent volume. F. A.

**PHILOSOPHY AND MEDICINE IN ANCIENT GREECE.** By W. H. S. JONES, Litt.D., F.B.A., Supplements to the *Bulletin of the History of Medicine*. No. 8. Pp. 100. Balt.: Johns Hopkins Press, 1946. Price, \$2.00.

THIS supplement of the *Bulletin* is the result of 8 years labor by the well-known Greek scholar and translator of the works of Hippocrates (Loeb Classical Series), aided by F. M. Comford until the latter's death. Section 1 (25 pages) considers briefly the Pre-Hippocratics, Plato and the Hippocratic Corpus. Section 2 is an essay on Hypothesis in Greek thought and on Philosophy and Medical Etiquette. Section 3, by far the

largest part of the study, is devoted to the Hippocratic "Ancient Medicine." Following an interesting Introduction, are given the Greek text, a translation with comments and several pages of additional notes. Indications of erudition are obvious in this production; the style, like that of the original Greek, is clear and terse. The translation differs but little from that of the Loeb volume. This Supplement will be received as further evidence of Dr. Sigerist's wisdom in organizing this series of Supplements and of the Institute's success in productive research in medical history. E. K.

**GYNECOLOGY WITH A SECTION ON FEMALE UROLOGY.** By LAWRENCE R. WHARTON, Ph.D., M.D., Asst. Prof. of Gynecology, The Johns Hopkins Medical School. 2nd ed. Pp. 1027; 479 ills. Phila. and London: Saunders, 1947. Price, \$10.00.

THE author has admirably incorporated a 247 page section on female urology into a clearly written textbook of gynecology. The presentation is concise and largely limited to fundamentals.

This edition has been improved over the 1st by 35 more illustrations and by the re-writing and rearrangement of a number of sections to clarify and expand original subject material and to include recent advances. New chapters on gynecologic diagnosis and embryology, and one by Dr. C. R. Prince on "Water Cystoscopy" deserve special mention. G. H.

**HARVEY CUSHING.** By JOHN F. FULTON. Pp. 754; 99 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, \$5.00.

FOR many more than his numerous admirers Harvey Cushing was, in Sherrington's words, "the most distinguished surgeon in this country, if not in the world"—this coming at a time when American surgery was forging most rapidly ahead to a leading world position. As this study well demonstrates, he was also a zealous educator, the book itself owing something, as will be seen below, to his desire to help medical students. Cushing was highly skilful as an operator and still more distinguished as a student of disease and of ways of recognizing and overcoming it. His artistic and literary gifts were of a high order; he was a discriminating bibliophile with a long enough purse to

satisfy his desire to bring together a notable library of important rare medical books. The history of medicine was to him a valuable discipline as well as a lifelong field of interest. Such a versatility of eminence offers great opportunity to a biographer, if adding correspondingly to the responsibility of his task. There should be general agreement, however, that it has been well carried out by Dr. Fulton, who was early delegated as Cushing's literary executor, and has been at work on this biography, except for serious interruption by the war, since shortly after Cushing's death. Also a distinguished student of the nervous system, educator, bibliophile and book collector, medical historian and experienced writer, and on the same Faculty with Cushing for several years before his retirement, Fulton was an ideal man for the job.

The volume is constructed on much the same lines as Cushing's own biography of Osler, except that being in one volume the details of his clinical work, especially in its technical phases, have been purposely curtailed. The same chronologic approach has been followed, with H. C.'s age conveniently repeated on each recto and the month and year on each verso. The same kind of material is included as in the Osler volumes—with numerous excerpts from Cushing's voluminous diary and letters. The book is well embellished with close to 100 illustrations, many fortunately being of Cushing's attractive pen and ink sketches. The present volume does not suffer by comparison with the Osler—a big compliment, truly. We are indeed fortunate that two such distinguished medical men should live on in these intimate, simple yet revealing biographies.

Cushing's intense, scintillating character shines through almost every page, with its valleys as well as its heights, the latter presented without show, the former without evasion. For instance, when depressed from overwork at Harvard, he writes: "Able to do no studying for some time . . . suicide about only alternative . . ." The episode of his accusatory letter to Dandy about the acoustic nerve tumor work, which provoked a lifelong bitterness, is frankly met—though in a sympathetic way that helps the reader to a better understanding of this complex character. As one might expect, there are not a few similar incidents,

for this is not an account of a placid life. More frequent opportunity arises, however, to let events illustrate the thoughtfully generous side of Cushing's nature; his many kindly deeds to assistants and students and those in want or distress; the Oslers' reaction to his presence at the deathbed of their son, Revere—these are but a few of the many instances given with obvious zest by a biographer who evidently has tried not to be carried away by his great admiration for his subject.

Aware that a biography was to be prepared, Cushing characteristically made provision in his will for a subvention, which has permitted preparation of this handsome as well as adequate volume at extremely low cost for these days of costly publishing. The medical world at large, as well as the medical students whom he is said to have had primarily in mind, should profit accordingly.

E. K.

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PRINCIPLES OF THE CONTACT LENS. By H. TREISSMAN and E. A. PLAICE. Pp. 88; 40 ills. London: Henry Kimpton, 1946. Price 10s/6d net.

This is a clear and concise evaluation of contact lenses and should be of value to all those who prescribe them. There is an excellent chapter on the physiologic optics of contact lenses with a comparison of the optical merits of spectacle lenses as compared to contact lenses. The methods employed in fitting and testing contact lenses are adequately described. The factors are mentioned which militate against tolerance in wearing contact lenses, but unfortunately no solution has as yet been found for those patients who develop corneal edema.

F. A.

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CLINICAL METHODS OF NEURO-OPHTHALMOLOGIC EXAMINATION. By ALFRED KESTENBAUM. Pp. 400; 65 ills.; 20 tables. New York: Grune & Stratton, 1946. Price, \$6.75.

THIS is an excellent book and is highly recommended for neurologists and neurosurgeons, as well as ophthalmologists. The first 5 chapters deal with the physiology and pathology of the optic pathways. In the first chapter, a review is given of the anatomy of the optic pathway; the second

deals with disturbances in the visual fields; the next 3 treat disorders of the various portions of the optic pathway; namely, the optic nerve, the chiasm and the retrochiasmal portions of the optic pathway. The sections on chiasmal lesions and retrochiasmal lesions are especially well done. Following this, are chapters on paralysis of the ocular muscles and supranuclear paralyses, nystagmus and disturbances of the symmetrical eye movements, such as convergence and divergence. Chapter 10 deals with pupillary abnormalities and disturbances of accommodation. Chapter 11 includes alterations in the palpebral fissure and a group of miscellaneous disturbances, such as trigeminous nerve affections and the Kayser-Fleisher ring in pseudosclerosis. The final chapter is concerned with functional disturbances.

The general style of the book is good and the illustrations, though diagrammatic, are excellent. The only possible fault that can be found is the inclusion, probably for completeness, of a number of tests for differentiating the site of lesions in the optic pathways, which are generally conceded to have little clinical value. In practically every instance, however, the author has been careful to point this out. It is the most practical book on neuro-ophthalmology which has so far appeared in English. F. A.

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**URGENT SURGERY.** By JULIUS L. SPIVACK, M.D., LL.D., Associate Professor of Surgery, University of Illinois College of Medicine; Corresponding Member Mexican Academy of Surgery; Senior Attending Surgeon, Columbus Memorial Hospital, Chicago; Attending Surgeon, Oak Forest Infirmary. Vol. I. Pp. 714; 572 ills., 14 in color. Springfield, Ill.: Charles C Thomas, 1946. Price, \$10.50.

The purpose of this volume is not clear to the Reviewer nor does the title seem justifiable. The surgeon who is to do most of the procedures described in the text must be a trained operator, and there is little that he can learn from this book. The "casual operator" referred to, as for example when simple closure of a perforated ulcer is discussed, should certainly not be encouraged to undertake the "urgent" 2-stage perineal operation for imperforate anus or an internal choledochoduodenostomy. Spleno-

pexy under any circumstances can hardly be regarded as urgent nor can operations for cysts of the spleen.

In this day of rapid transportation it is inconceivable that a child with pyloric stenosis cannot be taken to a competent surgeon who has had basic surgical training and who, if he wishes to review the steps of an uncommon operation, will go to a source book containing more anatomic and physiologic detail than this one.

This volume therefore cannot be warmly recommended nor the title condoned in the light of the contents chosen. I. R.

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**THE EYE MANIFESTATIONS OF INTERNAL DISEASE.** By I. S. TASSMAN. Pp. 614; 243 ills., 24 in color. St. Louis: C. V. Mosby, 1946. Price, \$10.00.

This is a well-written and readable book on medical ophthalmology. Although in no sense an exhaustive treatise, it covers the field well and includes good references to the literature. F. A.

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**VICTORY OVER PAIN.** By VICTOR ROBINSON, M.D. Pp. 338; 47 ills. New York: Henry Schuman, 1946. Price, \$3.50.

This is a readable, instructive, lucid and entertaining history of anesthesia. The author tells a stirring tale and makes many of the great characters of the 19th century live again.

The publishers state "we are all aware that scientific advances have reached a point where they dominate the lives and destiny of everyone. With this awareness has come a natural desire to understand more fully the rôle and impact of science on our everyday life." Anesthesia is one of these "scientific advances," and Dr. Robinson portrays in fascinating detail the rôle that American, English, Scottish, French, German and Russian medical circles have played in the development of this science. Anesthesia is regarded by all thinking people as one of the major contributions of man to his fellow. This book recounts the hazards and disappointments of research, the numerous failures to recognize the significance of new observations and the struggles for fame and fortune that followed the introduction of general anesthesia. Numerous anecdotes and many letters make this one of the most

entertaining histories that the Reviewer has read. It can be recommended without hesitation to all who are interested in the progress of medicine, be they laymen or physicians.

P. D.

**OCULOREFRACTIVE CYCLOPEDIA AND DICTIONARY.** By THOMAS G. ATKINSON, M.D., B.S.C. 3rd ed. Pp. 388. Chicago: Professional Press, 1944. Price, \$5.00.

This is a dictionary of ophthalmologic terms in which some of the terms are merely defined and others are expanded into encyclopedic references. This makes such a discrepancy in the value of the book for reference that it partially destroys its usefulness. Under Ptosis for instance, there is merely a sentence defining the condition, whereas 11 pages are given to the heading, Psychology of Vision. The book does contain a considerable amount of interesting material which is not readily available in other sources, but it is very uneven.

F. A.

**PENICILLIN: ITS PRACTICAL APPLICATION.** By 30 British Practitioners and Researchers. Edited by SIR ALEXANDER FLEMING, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S., Professor of Bacteriology in the University of London. Pp. 380; 59 figs. Philadelphia: Blakiston, 1946. Price, \$7.00.

THE name of Fleming attached to a book on Penicillin is enough to arouse great expectations. As far as the historical background, general principles, and the bacteriologic aspects are concerned, these expectations will be realized; the 2 chapters on these topics were contributed by Sir Alexander himself. The chapters on Chemistry and Manufacture, Pharmacy, Pharmacology, and Methods of Administration are also well done and reasonably adequate, as of the spring of 1946 in Great Britain. These, with Fleming's 2 chapters, occupy the first 104 pages and constitute the General Section. The remaining 21 chapters comprise the Clinical Section and are written by 24 specialists, including a dentist and a veterinarian who contribute appropriate discussions. As would be expected, there is considerable overlapping and unevenness in quality of coverage. The American reader will probably find the discussions of the treatment of syphilis quite inadequate, will

be confused at the lack of mention of any but British Pharmacopoeial preparations, and disappointed at the absence of adequate discussion of the different penicillins and the problem of producing them naturally or synthetically. The literature cited at the end of each chapter is largely British, which is perfectly proper and understandable but not extremely helpful for the American practitioner seeking further information than that given here. It probably is time for an international volume on penicillin.

C. S.

**ADVANCING FRONTS IN CHEMISTRY. II. CHEMOTHERAPY.** Edited by WENDELL H. POWERS, Assistant Professor of Chemistry, Wayne University, Detroit. Pp. 156; 6 figs. (photographs of contributors). New York: Reinhold Publ. Co., 1946. Price, \$3.25.

THIS presents 6 of 7 lectures given at Wayne University in 1945, as a Symposium on Chemotherapy. They are: Chemotherapy in Experimental Tuberculosis, by W. H. Feldman, V.M.D., Sc.D.; Synthetic Antispasmodics, by F. F. Blicke, Ph.D.; Chemistry of the Sulfa Drugs, by E. H. Northey, Ph.D.; The Antimalarial Problem, by H. S. Mosher, Ph.D.; Organometallic Compounds as Chemotherapeutic Agents, by C. K. Banks; Past Developments and Present Needs in the Chemotherapy of Parasitic Diseases, by Col. W. H. Wright, V.M.D., Ph.D. The 7th lecture was on Antibiotics, by Dr. H. E. Carter; actually the first of the series, it could not be prepared in time for publication, which is already more than a year after presentation. Feldman makes a good case for the value of the disulfone derivatives (Promin, Promizole, Diasone) against tuberculosis in guinea pigs but he clearly states that the results of trials in human patients are "not comparable to the striking results obtained in guinea pigs or to the dramatic effects with chemotherapeutic drugs in the treatment of patients who had such an acute disease as pneumococcus pneumonia." The inclusion of Synthetic Antispasmodics here is not covered by the definition of Chemotherapy used by the other contributors, nor is it justified by the brevity of the material presented. Northey's chapter on the sulfonamides is complete, well documented and up to date. Mosher's approach to the antimalarial problem is that

of an organic chemist whose interest lies in methods of synthesis; the recent synthesis of quinine is not covered nor is the now available result of the extensive work done along these lines under the O. S. R. D. during the war. Banks' chapter on the metals is a brief and reasonably adequate summary of the development of organic derivatives of arsenic, bismuth, antimony, mercury and silver. Col. Wright's chapter is long (41 pages), but it is the only part of the book that is likely to be valuable to the practitioner.

C. S.

**SQUINT AND CONVERGENCE.** By M. A. STUTTERHEIM. Pp. 95; 41 ills. London: H. K. Lewis, 1946. Price, \$3.00.

FROM start to finish, this book is a compilation of loosely thought-out ideas, badly expressed. The author is correct in his statement that at present we know very little about concomitant squint; but his original thoughts on the subject have meager foundations of fact and he blithely passes by all facts which are not in conformity with his theory. The book is of interest because of its novelty, but it cannot be regarded as a serious exposition of the subject. It is the type of book which usually comes from the pen of non-medical practitioners, and should only be read by someone with sufficient intelligence and background to interpret it critically.

F. A.

**DISEASES OF THE RETINA.** By HERMAN ELWYN, M.B. Pp. 587; 170 ills., 19 in color. Philadelphia: Blakiston, 1946. Price, \$10.00.

THIS is a comprehensive text of those diseases of the eye of which the chief manifestations are in the retina, and of the retinal manifestations of general disease. Part I deals with diseases of the retina resulting from disturbances in circulation, and deals extensively with the hypertensive retinopathies. The Author has written extensively on this subject in recent journals; in view of his authoritative position, it is surprising to find no mention made of Wagener's work in this section. His views on the origin of the retinopathy in diabetes are original; and, although they may not be accepted generally, are stimulating.

Part II deals with diseases of the retina resulting from vascular malformations. He

includes in this section a description of Coat's disease, which is again based on an original point of view that the fundamental pathologic factor in Coat's disease is a vascular malformation involving the small vessels with the formation of miliary aneurysms. The changes in these small vessels are interpreted by Elwyn to conform to our conception of a telangiectasis. Sturge-Weber disease is also included in this section. Elwyn believes the glaucoma found in this disease, as part of the clinical picture, is due to an angioma of the choroid.

Part III deals with the degenerative diseases of the retina on an hereditary basis. Part IV deals with inflammatory diseases of the retina; Part V with tumors of the retina; Part VI with diseases of the retina leading to retinal detachment; Part VII with developmental anomalies of the retina, and Part VIII describes radiation injuries of the retina.

The book is carefully written and well illustrated and is an outstanding contribution to our literature. It will be useful not only to the ophthalmologist, but also to the neurologist, the internist and the general practitioner, for the ophthalmoscope has now become part of the diagnostic equipment of all well-trained physicians.

F. A.

**PERIPHERAL VASCULAR DISEASES.** By EDGAR V. ALLEN, B.S., M.A., M.D., M.S., F.A.C.P.; NELSON W. BARKER, B.A., M.D., M.S., F.A.C.P.; and EDGAR A. HINES, JR., M.D., B.S., M.A., M.S., F.A.C.P., with Associates in the Mayo Clinic and Mayo Foundation. Pp. 871; 386 ills. Philadelphia: Saunders, 1946. Price, \$10.00.

THIS important book will be of value to the physician in general practice, the specialist in peripheral vascular disease, and the research worker. It contains an unusually complete presentation of the basic anatomy and physiology. The clinical material is based upon the wide experience of the authors, working in the Mayo Clinic, and contains an excellent review of the pertinent literature. Care is taken to distinguish between that which can be considered established, that which is opinion, and that which is mere hearsay. The illustrations are excellent and well chosen. While



the text is long for complete reading, an adequate index facilitates reference. It is highly recommended. J. G.

**THE NORMAL ENCEPHALOGRAM.** By LEO M. DAVIDOFF, M.D., and C. G. DYKE, M.D. Pp. 232; 155 ills. Philadelphia: Lea & Febiger, 1946. Price, \$5.50.

THIS is an exceptionally well-handled treatise on the technique of pneumo-encephalography and on the interpretation of the films obtained from the procedure. The most valuable information presented is the clear and direct correlation between the anatomic brain structures and their respective representations to shadows on the Roentgen ray film.

The untimely death of Dr. Dyke is indeed regrettable. Without him we are deprived of the sequel of this work; namely, the abnormal encephalogram. J. C.

**LA CULTURA IN VITRO DEL MIDOLLO OSSEO,** Problemi di Fisiopatologia Ematologica Studiati con la Tecnica della Cultura dei Tessuti. By AMINTA FIESCHI and GIOVANNI ASTALDI. Preface by CESARE FRUGONI. Biblioteca Hematologica, VIII, Directed by ADOLFO FERRATA. Pp. 309; 123 text figs. and 10 plates in color. Pavia: Tipografia del Libro, 1946. Price not given.

DURING the decade in which the senior author of this book has been a student of the tissue culturing of the hematopoietic organs, she has elaborated a new method which in her hands appears to give special advantages and permits combination with the Warburg technique for the investigation of tissue metabolism. Though she has paid special attention to the megaloblasts, pernicious anemia, and the leukemias, the 10 chapters cover various other phases of the subject, Cooley's anemia, for example. The old question of the genesis and evolution of the megaloblast furnishes an illustration of the capable way in which the subject matter is handled; being pupils of Ferrata, the authors perhaps naturally straddle the dilemma by upholding its evolution into a normoblastic-like cell.

The illustrations, as we have come to expect in Italian works on hematology, are excellent and demonstrate the technical skill shown both in the preparations and the

reproductions. These illustrations, together with the fortunate similarity of hematologic terms in Italian and English, make this volume of considerable value even to those who do not read Italian.

The purely morphologic approach to hematologic problems—carried to its extreme by the Germanic school of the past generation led by Naegeli and Pappenheim—has long been recognized as inadequate for further progress. Studies like this one—and we are pleased to see in the Bibliography the number of references to the functional approach written in English—augur well for the further progress in hematology along new dynamic approaches. E. K.

**ALLERGY.** By ERICH URBACH, M.D., and PHILIP M. GOTTLIEB, M.D. 2nd ed. Pp. 968; 412 ills. New York: Grune & Stratton, 1946. Price, \$12.00.

BECAUSE of the great amount of recent work in this field, the new edition represents extensive revision, with many new references and illustrations. Among the additions are sections on psychosomatic allergy, Rh factor, and allergic bronchitis. The important section on drug allergy has been enlarged and brought up to date, and descriptions of test methods have been amplified. The new format is attractive.

This is a valuable book and is strongly recommended. M. McC.

**THE HUMAN FRONTIER.** By ROGER J. WILLIAMS. Pp. 314; 5 figs. New York: Harcourt, Brace, 1946. Price, \$3.00.

THIS book is by the biochemist who discovered and synthesized pantothenic acid of the B vitamin group, and who now wants man studied in his entirety rather than separate parts. Urging the need for many more trained workers, he says: "It will be impossible to make serious advances in psychosomatic medicine as long as man-in-the-abstract remains the consistent theme . . ." The more important chapters are: Fundamental Metabolism as It Is Related to Character Traits. Endocrine Glands and Behavior. Psychological Traits and Capacities. Marriage. Criminology. Heredity and Environment.

If 2 animals who by inheritance should possess like anatomic structures for producing like metabolism the same way, develop

differences in their anatomies, then differences will be shown in their metabolisms. The dozen or more endocrine structures in all probability release some 40 different hormones; the thyroid and pancreas are recognized as producing 1 each, whereas, the pituitary may produce from 6 to 10. The effects of World War II will greatly enhance the future of psychology. The obvious thing about common sense is its wide appeal. In the concrete problem of marriage, the amount of verifiable information is exceedingly scant and fragmentary. Scopolamine, loosely referred to as "truth serum," depresses the higher brain centers, thus rendering the subject unable to "make up a lie or follow through in deception." Hope is expressed for its greater use, together with that of related substances. As to Heredity and Environment, the most promising field for study is identical twins, reared in different environments. Fortrightly, we are told of our shortcomings, which should be stimulating.

N. Y.

**THE VITAMINS IN MEDICINE.** By FRANKLIN BICKNELL, D.M., M.R.C.P., and FREDERICK PRESCOTT, M.Sc., Ph.D., A.R.I.C., M.R.C.S., Clinical Research Director, The Wellcome Foundation, London. 2nd ed. Pp. 916; 208 ills. New York: Grune & Stratton, 1946. Price, \$12.00.

THIS book is a valuable reference text on the vitamins. It has grown considerably in the 4 years since its first publication in December 1942, having increased from 662 to 916 pages, and from 120 to 208 excellent illustrations. All this despite wartime shortages and restrictions on printing.

The general form is similar to that of the 1st edition. Each vitamin is considered in a separate chapter. The approach is basically clinical but large subdivisions are devoted to such subjects as the history, chemistry, distribution in foods, experimental studies and human requirements, as well as a description of the diseases associated with deficiency, laboratory and therapeutic methods useful in practice. Each part is complete and well written. Documentation is elaborate: there is a large Bibliography at the end of each chapter; the whole totals over 4500 references.

The sections on the vitamin B complex and riboflavin have been rewritten and expanded.

Here has been collected together in an easily readable form a great fund of information otherwise unavailable. As a reference work this book will have important value for both students and practitioners. W. S.

**MEDICAL CLINICS OF NORTH AMERICA.** Chicago No. Symposium on Advances in Clinical Medicine. January 1947. Pp. 1-258. Phila: Saunders, 1946. Price, \$16.00 a year.

THIS volume is prepared especially for the general practitioner. Consequently such common and important conditions as hypertension, coronary disease, nephritis, peptic ulcer, the acute infectious diseases, the dysenteries, pneumonia and rheumatic fever are discussed.

A conservative evaluation of benadryl and pyrabenzamine is made. One clinic is devoted to the action of radioactive phosphorus and the alkylamines in the treatment of neoplastic and allied diseases of the hematopoietic system.

The electrocardiographic studies of Katz and Weinstein are interesting. Chronic hypoparathyroidism; encephalitis disseminated lupus erythematosus, steatorrhea and same phases of psychosomatic medicine are excellently considered.

J. W.

**UTERINE CONTRACTILITY IN PREGNANCY.** By DOUGLAS P. MURPHY, M.D., F.A.C.S., Asst. Prof. of Obstetrics and Gynecology, and Research Associate in the Gyneccean Hospital Institute of Gynecologic Research, Univ. of Penna. Pp. 134; 64 ills. Phila.: Lippincott, 1947. Price, \$5.00.

THIS monograph presents Dr. Murphy's extended work in the study of uterine activity in pregnancy and labor.

Over 3000 records have been taken with the Lorand tocograph during pregnancy and labor from 1153 individuals. These tocographic records provide a graphic representation of the frequency and character of uterine contraction and the tonus of the uterus at various periods from the time the uterus is first palpable above the pelvic inlet in pregnancy until the placenta and the fetus have been expelled in labor. The results have been carefully sorted, statistical data based thereon, and conclusions reached which are conservative, and in many phases of the subject, conclusive. The monograph

therefore constitutes an authoritative statement on this very important phase of obstetric physiology. It is a book which should be in the hands of all obstetric teachers, and its comment and suggestions should be of practical use to the obstetric clinician. The reader is impressed so much by the potential clinical value of the *Lorand toco-graph* in the observation of abnormal labor that he wishes this instrument were commonly available for practical usage.

Dr. Murphy states that he set out primarily to study the activity of the uterus in pregnancy. His investigations have shown (1) a period of relative quiescence until the 34th week of gestation or until approximately 6 weeks before term, (2) a period of non-rhythmic activity from the 34th to 39th week of pregnancy, and (3) a period of rhythmic activity which includes the 39th and 40th weeks of pregnancy. Regular, rhythmic contraction during this last period has some bearing upon a prompt normal delivery.

Probably the parts of greatest interest to the clinician are those which have to do with the effect of pituitary extract upon uterine activity, and those which concern primary uterine inertia. No response to pituitary extract before the 7th month has been noted. After that time a certain number of uteri respond in more or less characteristic fashion while others continue completely unresponsive. The response appears to vary with the size of the dosage and with the preëxisting tone of the uterus. The responses may be (1) clonic, (2) incomplete tonic and (3) complete tonic. Unfavorable tonic reactions are avoided by administering the drug where there is high tone of the uterus.

Dr. Murphy's findings in primary uterine inertia concur with those of Lorand in demonstrating inefficient, irregular, feeble uterine activity in this syndrome. He is in accord also with the classification which has been presented by Lorand of 3 types of primary uterine inertia: (1) hypotonic, (2) isotonic and (3) hypertonic, depending upon the degree of uterine tone associated with this condition. The treatment of these various types of inertia is discussed.

There are many other observations and conclusions in this monograph which have clinical as well as academic interest to the specialist in obstetrics.

T. M.

**RADICAL SURGERY IN ADVANCED ABDOMINAL CANCER.** By ALEXANDER BRUNSCHWIG, M.D., Prof. of Surgery, Univ. of Chicago. Pp. 324; 116 ills.; 16 tables. Chicago: Univ. of Chicago Press, 1947. Price, \$7.50.

It is fortunate that surgeons, in general, may concentrate their attention on the immediate surgical problems presented by their patients else many surgical advances would be lost in the inactivity resulting from insoluble philosophic and economic considerations. As a rule, both patients and their families are ready and even eager to have any procedure done that may offer a chance, however slight, for survival so that the decision to attempt wide excision of malignant lesions need not rest upon the surgeon alone.

The author discusses the extension of surgery to include operations on "inoperable" malignant abdominal lesions and is able to present results that certainly justify his decision to operate, for of the 100 patients he reports there are 13 living and well, with an average survival time of 40 months. Most of the operations he describes were of such extent that they may be attempted only by experienced surgeons, so that it can be assumed that it is unnecessary to caution against such radical procedures being undertaken without a well-laid plan of action, both as to the operation and to the care of the patient.

The monograph will be of great interest to all surgeons but of usefulness only to the few who have sufficient training and skill, as well as hospital facilities, to carry out such extensive surgical procedures.

I. R.

**OFFICE ENDOCRINOLOGY.** By ROBERT B. GREENBLATT, B.A., M.D., C.M., Prof. of Endocrinology, Univ. of Georgia School of Medicine; Director, Sex Endocrine Clinic Univ. Hosp., Augusta, Ga. 3rd ed. Pp. 306; 71 figs. Springfield, Ill.: Charles C. Thomas, 1947. Price, \$4.75.

THE 1st edition of this small book appeared in 1941 as an outline guide for office practice in endocrinology, having originally been based on a series of postgraduate lectures by the author. Despite the implication of its title, the 46 short chapters deal almost exclusively with gynecologic endo-

crinology. The text is often repetitive and wordy. Emphasis is uneven and the style varies from the excessively lyrical to almost telegraphic English. The occasional specific endorsement of certain commercial products by name seems in questionable taste. Some of the therapeutic recommendations (e. g., that of the efficacy of orally administered pituitary preparations) appear somewhat extravagant. The unfortunate practice of printing category headings and numerical bibliographic references in identical type is often confusing. The book does not seem to be an important contribution to current endocrinologic literature.

E. R.

**PENICILLIN IN SYPHILIS.** By JOSEPH EARLE MOORE, M.D., Associate Prof. of Medicine and Adjutant Prof. of Public Health Administration, Johns Hopkins Univ.; Physician-in-Charge, Syphilis Division of the Medical Clinic and Visiting Physician, Johns Hopkins Hosp.; Chairman, Syphilis Study Section, National Institute of Health, U. S. P. H. S.; Chairman, Subcommittee on Venereal Disease, N. R. C. Pp. 284; 58 figs; 52 tables. Springfield, Ill.: Charles C Thomas, 1947. Price, \$5.00.

IN the battle of "Scientists Against Time," one of the outstanding developments in medicine during the recent war was the discovery in June 1943, by Mahoney, Arnold and Harris, of the United States Public Health Service, that penicillin had definite antisymphilitic powers. This fact, plus the relatively non-toxic character of the preparation, seemed to be just what was needed for the handling of early syphilis in the Armed Forces. A concentrated co-operative group study of penicillin in syphilis was undertaken by the United States Army, Navy, Public Health Service, and the Committee on Medical Research of the Office of Scientific Research and Development, under the general auspices of a Penicillin Panel appointed by the Subcommittee on Venereal Diseases, National Research Council. In addition, some 25 civilian clinics participated in a program of study of the effect of penicillin in early and late syphilis. Lately, the study has been taken over by the Syphilis Study Section of the National Institute of Health. It is particularly fortunate that Dr. Joseph Earle Moore, who coordinated the various aspects of this

program, has prepared this *interim* statement of the present knowledge of the value of penicillin in syphilis therapy. As he has access to much as yet not formally published data, this book is unique in the field in not appearing stillborn. Changeable as is the subject of penicillin in syphilis, the material presented will be still fresh for some time to come. Another valuable feature is that while the author has cited most of the contributions of others, some of the sections represent a definitive personal interpretation on the subject by Moore. A notable example of this is the discussion of the treatment of neurosyphilis.

This book tells the physician what to do as well as what not to do with penicillin in syphilis. Unfortunately, the style of presentation is for the most part too statistical for the average reader. It would at least make the subject more appealing if individual case reports were more generally interlarded through the text and its many graphs.

The author (p. 212) reiterates the statement made by him and Goodwin recommending "*that for the purpose of prevention of prenatal syphilis, metal chemotherapy for the syphilitic mother, whether with early or late (including latent) syphilis, be abandoned and that penicillin be adopted universally instead.*" We believe that this conclusion based on a variety of considerations may become one of the most firmly established results of the penicillin study, but, in a field so young, such dogmatism may force an otherwise conscientious physician without adequate hospitalization facilities required by penicillin therapy, to adopt a compromise system of penicillin prenatal therapy, which may prove inadequate.

H. B.

**PSYCHOBIOLOGIC FOUNDATIONS IN DENTISTRY.** By EDWARD J. RYAN, B.S., D.D.S., EDITOR, Oral Hygiene and The Dental Digest. Pp. 131. Springfield, Ill.: Charles C Thomas, 1946. Price, \$3.00.

THE healing professions have been dominated to such an extent by the scientific method that common sense observation and understanding of man as an entity rather than a complex of signs and symptoms has tended to be forgotten. Dentistry, with its emphasis on technical excellence and its mechanical appliances, has not infrequently lost sight of the patient toward whose wel-

fare the dentist's knowledge and skill were directed.

Dr. Ryan has had much experience as an editor in writing for large groups of practicing dentists. He writes clearly and presents his subject in an interesting and thought-provoking manner. He has selected wisely from the literature on psychosomatic medicine and has adapted principles for application to dental practice. He is concerned particularly with the reaction of the dental patient to pain and makes suggestions which should be of value to practitioners in meeting this problem. A chapter is devoted to the interpretation of constitutional patterns of disease with particular reference to the influence of emotions upon the tissues of the mouth. Dental disease in the 7 ages of man is discussed and modifications of treatment indicated in every age group are suggested.

This book should be widely read and should stimulate dentists to further study of the principles of psychobiology and their applications to dentistry. P. B.

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**CONDUCTION ANESTHESIA: CLINICAL STUDIES OF GEORGE P. PITKIN, M.D.,** edited by JAMES L. SOUTHWORTH, M.D., and ROBERT A. HINGSON, M.D. Pp. 981; 606 ills. Philadelphia: J. B. Lippincott, 1946. Price, \$18.00.

For years Dr. George Pitkin collected artists' drawings illustrating techniques of regional anesthesia. Thousands of dollars were expended during his lifetime. These plates, skillfully executed and superbly reproduced, form the basis of this volume.

Anatomy is carefully presented in an introductory 212 page section. The pharmacology of local anesthetic agents is discussed, after which detailed considerations of all types of conduction anesthesia are given in the central section of the book. Concluding chapters are devoted to caudal, spinal and refrigeration anesthesia, and there is a final section on the therapeutic applications of nerve block. The format is pleasing, the paper excellent and the only suggestion the Reviewer has as far as the book itself is concerned is that a 2 volume edition would be easier to handle than the rather bulky single volume.

The work should be of real interest to anesthesiologists and to surgeons engaged both in the practice of general surgery or in the

surgical specialties such as neurosurgery, otolaryngology, orthopedics and ophthalmology. It certainly is detailed, perhaps too detailed. For example, the discussion of block of the brachial plexus includes a posterior, infraclavicular, axillary, lateral and supraclavicular approach.

The section on spinal anesthesia covers 100 pages. Some statements are made which might be challenged. Thus, the Sylvester method is recommended for production of artificial respiration in instances of respiratory distress and oxygen administration via an anesthesia machine is not mentioned. The dosage of procaine for use in obstetrics is given as 100 to 200 mg. which seems excessive.

In the Reviewer's opinion, it constitutes a comprehensive coverage of all forms of regional anesthesia, but its very comprehensiveness may limit its value to all but the specialist. R. D.

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## NEW BOOKS

*Diseases of the Chest, Emphasizing X-ray Diagnosis.* By ELI H. RUBIN, M.D., F.A.C.P., F.C.C.P., and MORRIS RUBIN, B.A., M.D. Pp. 685; 355 ills., 24 in color. Phila. and London: Saunders, 1947. Price, \$12.00.

*Medical Aspects of Growing Old.* By A. T. TODD, M.B. (Edin.), M.R.C.P. (Lond.). Pp. 164. Balt.: Williams & Wilkins, 1946. Price not given.

*Handbook of Medical Emergencies.* Contributors: THOMAS B. FITZPATRICK, M.D., JOHN L. BAKKE, M.D., H. STANLEY BENNETT, M.D., EVAN CALKINS, M.D., EDWARD A. CARR, JR., M.D., DEAN P. APPERSON, M.D., WALTER W. POINT, M.D., and JAMES M. STEWART, M.D. Pp. 106. Cambridge: Harvard Univ. Press, 1947. Price, \$2.50.

*Milk and Food Sanitation Practice.* By H. S. ADAMS, D.Sc., Division of Public Health, Minneapolis. Pp. 311; 65 ills. New York: Commonwealth Fund, 1947. Price, \$3.25.

*Recent Progress in Hormone Research.* Proceedings of the Laurentian Hormone Conference. Edited by GREGORY PINCUS. Pp. 399; 29 ills. New York: Academic Press, 1947. Price, \$7.50.

Thirteen articles, mostly by well-known investigators, including considerable unpublished material.

## BOOK REVIEWS AND NOTICES

*Health and Rehabilitation Through Chest Training.* By SAMUEL DELANO, A.B., M.D. Pp. 142. New York: William-Frederick Press, 1947. Price, \$2.50.

*Office Immunology, Including Allergy.* Edited by MARION B. SULZBERGER, M.D., and RUDOLF L. BAER, M.D. Pp. 420; 6 ills. Chicago: Year Book Publishers, 1947. Price, \$6.50.

THE 17th of the General Practice Manuals. *Psychiatric Research.* Papers read at the Dedication of the Laboratory for Biochemical Research, McLean Hosp., Waverly, Mass. By CECIL K. DRINKER, JORDI FOLCH, STANLEY COBB, HERBERT S. GASSER, WILDER PENFIELD and EDWARD A. STRECKER. Pp. 113. Cambridge: Harvard Univ. Press, 1947. Price, \$2.00.

*Biological Symposia. Estimation of the Vitamins.* Vol. XII. Edited by JACQUES CATTELL. Pp. 531. New York: Ronald Press, 1947. Price, \$6.50.

THIS volume is a collection of papers by well-qualified investigators dealing with the best recognized vitamin assay methods. The types of biologic assay that use animals, microbiologic methods that use microorganisms, and the physicochemical methods are treated by different authors. The collection fills a gap in the vitamin literature and will be extremely useful for reference in this field. (W. S.)

*Hypnotism Today.* By LESLIE M. LECRON, B.A., and JEAN BORDEAUZ, B.A., M.A., Ph.D., Consulting Psychologists and Psychotherapists. Foreword by MILTON H. ERICKSON, M.D., Director of Psychiatric Research, Wayne County Hosp., Eloise, Mich. Pp. 278. New York: Grune & Stratton, 1947. Price, \$4.00.

WRITTEN by 2 psychologists, "Hypnotism today" is an enthusiastic presentation of the history, theory, technique and practical therapeutic uses of hypnosis. As Dr. Erickson states in the Foreword, the authors "have selected their material well, . . . and their presentation of their own studies is unassuming and straightforward." (W. P.)

## NEW EDITIONS

*Standard Methods of the Division of Laboratories and Research of the New York State Department of Health.* By AUGUSTUS B. WADSWORTH, M.D. With a Foreword by GILBERT DALLDORF, M.D. 3rd ed. Pp. 990; 105 ills. Balt.: Williams & Wilkins, 1947. Price, \$10.00.

*A Textbook of Medicine.* Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., with the assistance of WALSH McDERMOTT, M.D., HAROLD G. WOLFF, M.D. 7th ed. Pp. 1730; 244 ills. Phila., and London: Saunders, 1947. Price, \$10.00.

THIS hardy perennial exhibits its customary excellence in spite of the difficulties of wartime. Articles have been inserted on 16 new subjects, and there are some 50 or 60 new write-ups, occasioned by death or retirement of former contributors.

*Theory of Occupational Therapy.* By NORAH A. HAWORTH, M.A., and E. MARY MACDONALD. Foreword by SIR ROBERT STANTON WOODS, M.D., Physician-in-Charge of Dept. of Physical Medicine, London Hospital. 3rd ed. Pp. 159; 6 ills. Balt.: Williams & Wilkins, 1947. Price, \$2.50.

*Vascular Disorders of the Limbs.* By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., etc., Physician-in-Charge of Dept. of Clinical Research, Univ. College Hosp., London. 2nd ed. Pp. 118. New York and London: Macmillan, 1946. Price, \$2.25.

*Diseases of Metabolism. Detailed Methods of Diagnosis and Treatment.* A Text for the Practitioner. Edited by GARFIELD G. DUNCAN, M.D., Director of Med. Div., Penna. Hosp.; Clinical Prof. of Medicine, Jefferson Medical College. 2nd ed. Pp. 1045; 167 figs. Phila. and London: Saunders, 1947. Price, \$12.00.

MUCH has transpired in the field of metabolism in the 5 years since the 1st ed. appeared. The most extensive changes are the sections on the Thyroid Gland, the Kidneys, the Blood, the Endocrines, Alloxan Diabetes.

*The Principles and Practice of Medicine.* (Originally written by WILLIAM OSLER.) By HENRY A. CHRISTIAN, A.M., M.D., LL.D., etc. Hersey Prof. of the Theory and Practice of Physic, etc. 16th ed. Pp. 1539. New York and London: D. Appleton-Century, 1947. Price, \$10.00.

VIGOROUSLY proceeding into its second semi-centennial, this classic among medical textbooks remains the leading exponent in its field of single authorship. It has kept well abreast of the considerable additions to medical knowledge since the last edition (1914), with preservation of a "continuity of thought and a balance in description" difficult to obtain in books written by a large body of authors.

*Clinical Practice in Infectious Diseases.* By E. H. R. HARRIES, M.D. (LOND.), F.R.C.P., and M. MITMAN, M.D. (LOND.) F.R.C.P. 3rd ed. Pp. 679. Balt.: Williams & Wilkins, 1947. No price given.

*Pye's Surgical Handicraft.* Edited by HAMILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hosp., London, etc. 15th ed. Pp. 668; 789 ills. Balt.: Williams & Wilkins, 1947. Price, \$6.00.

THIS manual, first published in 1884, is a practical, well-illustrated handbook that contains in brief form a vast quantity of information. The surgical resident in America will find it somewhat lacking in its neglect of physiologic principles, as for example the nutrition of a patient with decubitus ulcers; but any resident can profit from studying the technical aids described for the care and comfort of patients.

*Diseases Transmitted from Animals to Man.* By THOMAS G. HULL, Ph.D., Director, The Scientific Exhibit American Medical Association. 3rd ed. Pp. 571; 75 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$10.50.

*Pulmonary Tuberculosis.* By R. Y. KEERS and B. G. RIGDEN, of the Red Cross Sanatoria of Scotland. 2nd ed. Pp. 277; 124 ills. Balt.: Williams & Wilkins, 1946. Price, \$5.00.

THIS small volume, intended by the authors as a handbook for the student and general practitioner, admirably serves its purpose. In 15 brief and concise chapters a summary of the essential knowledge on diagnosis and management of pulmonary tuberculosis is presented. It contains 114 excellent reproductions of chest roentgenograms illustrating the use of Roentgen ray in the differential diagnosis, assessment of progress, and therapy of tuberculosis.

*Psychopathology. A Survey of Modern Approaches.* By J. ERNEST NICOLE, O.B.E., L.M.S.S.A., D.P.M.R.C.P.C.S., Medical Supt., Winwick Mental Hospital. 4th ed. Pp. 268. Balt.: Williams & Wilkins, 1946. Price, \$4.75.

THIS handbook reviews briefly the different approaches to psychopathology. Freud and McDougall are given about the same space and physiologic and ethnologic findings are considered along with the theories of Kempf, Rivers, Watson, Kretschner. The outlines are clear and brief and there are useful cross-references. The Bibliography is extensive.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

SEPTEMBER, 1947

## ORIGINAL ARTICLES

### ON THE LATER DEVELOPMENT OF HEART DISEASE IN APPARENTLY HEALTHY PERSONS WITH ABNORMAL BALLISTOCARDIOGRAMS

EIGHT- TO TEN-YEAR AFTER-HISTORIES OF 90 PERSONS  
OVER 40 YEARS OF AGE

BY ISAAC STARR, B.S., M.D.

PROFESSOR OF THERAPEUTIC RESEARCH  
PHILADELPHIA, PENNSYLVANIA

(From the Department of Therapeutic Research, University of Pennsylvania)

BALLISTOCARDIOGRAMS were first taken in the University Hospital in 1936 and, as soon as we were thoroughly satisfied with the method,<sup>3</sup> work on the normal standards was begun.<sup>4</sup> It was soon apparent that, with foresight in designing our attack on the problem, a double purpose could be accomplished. By selecting our normal subjects from the permanent population of the hospital and medical school, and from relatives and friends established in Philadelphia, we would not only be able to define the normal record, but also, by keeping contact with the group for a period of years, be in a position to compare records obtained on subjects who believed themselves to be in good health with their after-histories. By such a study we could ascertain whether the ballistocardiograph could detect cardiac abnormality before the clinical picture developed, and learn to interpret what abnormalities we encountered.

Ten years have now elapsed since the first record of this series was taken. 8 years since the last. During this time the after-histories of a few cases have been mentioned<sup>5</sup> and a preliminary report made.<sup>6</sup>

In this publication we present the after-

histories of 90 persons who were between 40 and 85 years of age when tested in 1937-1939. Comparison between the original records and the after-histories has disclosed a striking correlation. A large proportion of those whose ballistocardiograms were unduly small, or abnormal in form, developed serious heart disease during the decade which followed.

**Method. Selection of Subjects.** We chose as our subjects only those who believed themselves to be in good health and gave no history suggesting cardiovascular disease or any chronic ailment except as follows: Several persons with a history of occasional seasonal asthmatic attacks and 2 cases of pulmonary tuberculosis who had been arrested for years were not excluded. More debatable is the inclusion of 2 subjects who had once had transient attacks of auricular fibrillation. Both had been carefully studied and no cardiac abnormality had been disclosed, and they considered themselves to be in excellent health. In addition, a few other instances of ill health preceding the tests are described in the case reports.

When testing the older subjects we sometimes discovered abnormal blood pressures of which they had been ignorant, and it was hard to decide what value should be accepted as normal in this older age group.



Those subjects with really high values were, of course, excluded from this series. We included 1 tense individual with a blood pressure of 170/100, thinking that the elevation was largely emotional. Aged 72, he was unusually athletic and considered himself in good health. All others included had pressures lower than this.

*Technique of the Test.* The ballistocardiograms were taken according to our standard technique,<sup>4</sup> i. e., with the subject recumbent and after a 15 minute rest period in this position. The blood pressure was taken also. No records were made within 2 hours after a meal.

weight of 280 gm. causing a deflection of 1 cm. Pulse rate is to be counted per minute and body weight expressed in pounds.

The value of K varies with the age of the subjects and it can be obtained from Table 1 which also gives the standard deviations as a measure of the scatter of the data. We were disappointed to find that the scatter is larger than when our old formula, containing the factor for aortic cross-section was used.<sup>4</sup>

When cardiac output, or simply the amplitude of ballistocardiograms, is referred to body weight it is far from certain how one should interpret results secured on persons

TABLE 1.—VALUES FOR K AND STANDARD DEVIATIONS DERIVED FROM A STATISTICAL ANALYSIS OF BALLISTOCARDIOGRAMS ON 163 PERSONS WHO DID NOT DEVELOP CARDIOVASCULAR DISEASE IN THE FOLLOWING 8 TO 10 YEARS

	Age (yrs.)	No. of cases	K	Scatter of data Sigma in % of mean
Using actual weight in pounds . . . .	20-29	54	232	16.7
	30-39	45	264	15.6
	40-49	41	282	22.7
	50-59	23	344	17.1
	60-69	9	344	21.5
Using ideal weight in pounds . . . .	20-29	54	229	14.5
	30-39	45	253	14.3
	40-49	41	289	18.5
	50-59	23	333	14.6
	60-69	9	363	19.0

*Calculation of Results.* In reviewing the series the original records were remeasured and the data recalculated. In the intervening years doubt has arisen concerning the use of the aortic cross-section area as a factor in the calculation of cardiac output.<sup>7</sup> Experiments to clarify the point have been delayed by war duties and have not yet been completed, so we tried various methods of calculation. Results obtained by the old "area formula"<sup>3,4</sup> were analyzed in a preliminary report<sup>6</sup>. In this paper we have used the "area formula" with the aortic factor omitted, altering the constants to give a figure which was a percentage deviation from the average of normal persons and not an absolute value. This formula was as follows:

$$\text{Percentage deviation from normal} = \frac{K_1 \sqrt{(2\int Idt + \int Jdt)}_1 \sqrt{C} \times \frac{\text{Pulse rate}}{\text{body weight}}}{100} - 100$$

To use this formula the areas of the I and J waves were measured as described in previous papers,<sup>3,4</sup> our ballistocardiograph being calibrated in the usual manner, a

too fat or too thin. For this reason the results were calculated both in terms of actual, and of ideal weight, the latter value derived from age and height according to actuarial data.<sup>2</sup>

The new formula can thus be used as a measure of the normality of any case, but a serious question should be raised first. Should the standard of normality for any person be derived from data obtained in his age group, or should the results be compared with those obtained in healthy young adults? Those favoring the first plan should use a different K for each decade of life; those believing in the second should use only one value for K, that obtained in the 20-29 age group. Inspection of the data inclines me to favor the second plan. By it many healthy persons over 50 years of age will be judged abnormal but the after-histories indicate that it is in this group that heart disease may be expected to occur with unusual frequency. And the fact that an older person has a circulation equal to that of healthy youngsters seems more

worth knowing than his relation to his own age group. But this conclusion might well be debated and only prolonged experience will permit a final decision on the point.

Needless to say, this formula is designed to estimate cardiac output relative to the normal, but our ability to detect cardiac abnormality does not depend on our ability to calculate cardiac output correctly, and the conclusions of this paper could be presented entirely without reference to cardiac output.

*Obtaining After-histories.* Continued contact with the great majority of the persons tested in 1937-1939 was an easy matter. When sick they came to the University Hospital in most instances. Six died in this hospital and necropsies were obtained on 3. Three died in other hospitals and detailed data could be obtained, but there were no necropsies. Two died suddenly and unexpectedly while going about their business.

When sick, the subjects usually consulted some member of the staff of the University Hospital. I am indebted to Dr. C. C. Wolferth, Dr. F. C. Wood, Dr. T. G. Miller and Dr. R. L. Mayock for placing records at my disposal.

Contact with those in good health was also easy as most were still working in the medical school or hospital. A few who had moved away were reached by letter.

**Results.** Typical ballistocardiograms secured in 1937, 1938 and 1939 are shown in Figure 1. The results of the calculation are given in Figure 2, where the after-histories are indicated by different symbols. In Figure 2 the results obtained on any subject can be related both to those obtained on subjects in the same age group and, by means of the scale to the left, to those secured on healthy persons between 20 and 30 years of age.

When ideal rather than actual weight is used there is less scattering of the data given in Figure 2, and for that reason this method of calculation seems preferable. In the case reports given below, ideal weight was used unless the reverse is stated. But, as a glance at Figure 2 will show, it makes no difference to the conclusions whether actual or ideal weight is employed as a standard of reference for the size of ballistocardiograms.

The results secured on the most interesting cases will now be presented in detail.

**SUBJECTS WHO GAVE BALLISTOCARDIOGRAMS ABNORMAL IN FORM.** Four of our subjects gave ballistocardiograms abnormal in form when tested between 1937 and 1939.

*Subject X. L.* always impressed me as a rather sluggish individual when I knew him in 1939. The record obtained then is shown in Figure 1. It is so confused that the identification of systole would be difficult for an inexperienced person. The form varies from beat to beat. K is the only conspicuous wave and both I and J are grossly abnormal in most complexes. X. L. was 46 years of age when this test was made and he thought of himself as in good health at that time.

X. L. worked steadily as a chemist for the next 8 years. Within a year before his death he had passed a life insurance examination and took out insurance. In the summer of 1946 a medical friend noted he was more dyspneic on exertion than before. In the fall of 1946 he received news of the death of his mother, and started for her home by motor. After traveling about 100 miles he complained of feeling badly and stopped the car before a drug store. His wife entered the store to obtain medicine for him, and when she returned he was lying dead over the wheel.

*Subject C. N.* was 48 when his record was obtained in 1937, and I would have judged him to be in excellent health, as he himself believed. This record was normal in all ways except one. The H wave approximately equalled the J wave in height in every complex, producing an abnormality of the "early M" type. At the beginning of my experience<sup>4</sup> I did not regard this as a serious abnormality, but I have seen it in increasing frequency in manifest coronary heart disease and have published some records of this type.<sup>5</sup>

C. N. suffered from an attack of cardiac infarction in 1940. The symptoms and electrocardiographic changes were typical. The course was mild and recovery practically complete. During the war he served with distinction in a job requiring chiefly desk work. At present he thinks it wise to avoid unusual exertion but he leads an active life and has no symptoms.

*Subject M. T.* had served as a technician in the hospital laboratory for over 20 years. He was 57 years old when tested in 1937, and considered himself in excellent health as did I. His ballistocardiogram was certainly not normal. The larger complexes of

after this test and I regained contact only after some difficulty. When I finally found him in 1947 he reported that he had remained in excellent health and denied all symptoms which might suggest cardiac disease. A second ballistocardiogram taken in

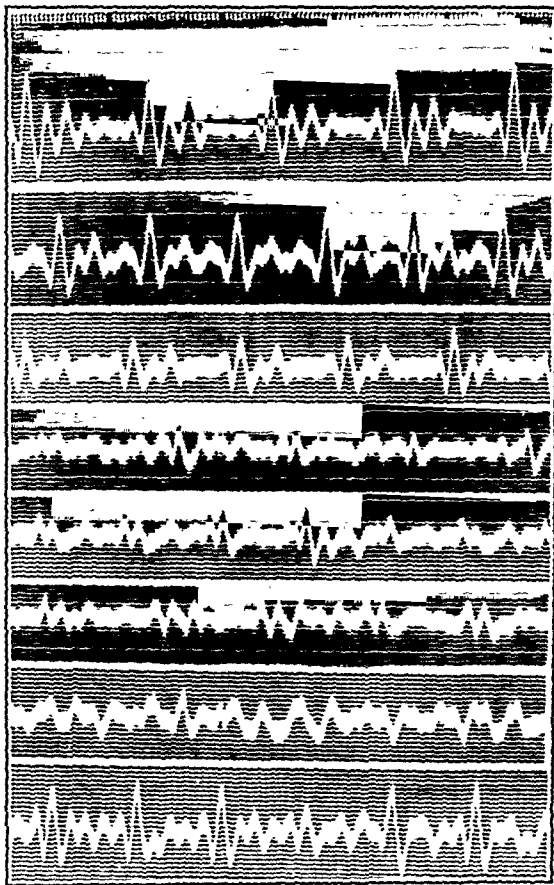


FIG. 1.—Ballistocardiograms taken on supposedly healthy persons in 1937, 1938 and 1939. *Top*—Record of O. C., aged 56. A normal record. He has remained in good health. *Second*—Record of, M. R., aged 79. A normal record with an unusual amplitude for his age. He is alive and active at present, aged 87. *Third*—Record of F. G., aged 59. Normal in form, amplitude below average normal for that age but not below the lower limits of normal. This subject developed angina pectoris. *Fourth*—Record of K. V., aged 74. A record much reduced in amplitude. The subject developed angina pectoris. *Fifth*—Record of G. E., aged 74. A record of abnormally small amplitude. He developed angina and died of cardiac infarction. *Sixth*—Record of D. G., aged 63. A record of abnormally small amplitude. He developed cardiac infarction 6 years later. *Seventh*—Record of X. L., aged 46. A record very abnormal in form. He dropped dead 7 years later. *Eighth*—Record of S. V., aged 61. A normal record. He dropped dead in 1945, necropsy showed cerebral hemorrhage and a normal heart. (Records reduced to three-fifths actual size.)

his typical respiratory cycle were either normal or nearly so, but the 3 or 4 smaller complexes were distorted, the I wave being small or absent and J wave so diminished in size that it hardly rose above the base line in many complexes.

M. T. left the University Hospital soon

1947 was quite similar to the first but perhaps not quite so abnormal as the percentage of abnormal to normal complexes was smaller than in 1937.

*Subject D. H.*, a physician, was 63 years of age when tested in 1937 and thought of himself as in good health, as did I. The

ballistocardiogram was very abnormal. Only an occasional large complex was normal in form. In the rest, the abnormality varied from beat to beat with the respiratory cycle. The most abnormal were of the typical late downstroke type with I very shallow and rounded, J low and wide and K deep and conspicuous. An occasional complex was so small that the waves were hard to identify. Various forms intermediate between these and the normal occurred in other complexes.

D. H. has written me that he had his first attack of coronary infarction in July 1940 and he describes it as moderately severe. A second such attack in June 1942 was described as slight, another in September of that year, as moderate. Further attacks in 1943 and 1945 were described as slight and moderate. Between these acute episodes there has been an occasional attack of angina pectoris. At present he has retired from practice, avoids undue exertion, and suffers

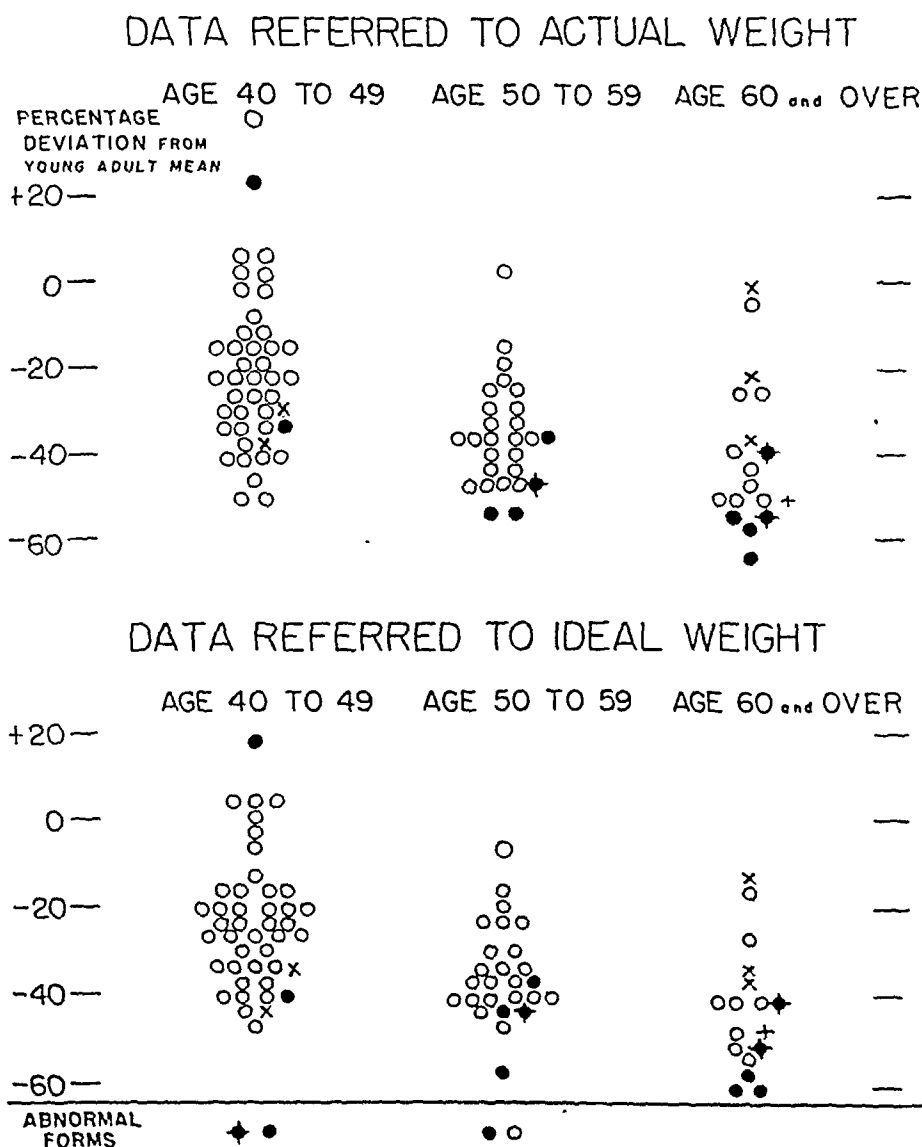


FIG. 2.—Comparison between the after-histories and the relative amount of the circulation as calculated from the time-amplitude of ballistocardiograms taken in 1937, 1938 and 1939. The data are referred to the subjects' actual weight in the upper diagram, to their ideal weight in the lower. The scale to the left is based, not on the data here given, but on the statistics of 54 healthy persons between 20 and 30 years of age. Zero has been placed at the mean of this group. The normal limits of this group, defined as twice the standard deviation, are  $\pm 33\%$  from the mean when referred to actual weight,  $\pm 29\%$  when referred to ideal weight. The different symbols indicate the after-histories— $\circ$ , remained well until 1947;  $\bullet$ , developed coronary heart disease;  $+$ , died of heart disease;  $\times$ , died without developing heart disease.

only from an occasional feeling of constriction in the chest. He has undue dyspnea if he performs any unusual exertion.

**SUBJECTS WHO HAD BALLISTOCARDIOGRAMS NORMAL IN FORM.** *Subjects Who Developed Heart Disease.* These are represented by black dots and crosses in Figure 2, and by records 3, 4, 5 and 6 of Figure 1. One sees at a glance that these cases had ballistocardiograms with systolic complexes smaller than most others of their age group, and conspicuously smaller than the records obtained on healthy young adults.

In Figure 2, where the data are referred to ideal weight, 4 of our subjects deviated from the average normal of the 20-29 age group by over 55%. These had smaller ballistocardiographic deflection than any other subjects tested, and their after-histories will be presented first.

*Subject F. D.* was 69 years of age when tested in 1937. He had suffered from asthma in his youth but had had no attacks for years, and considered himself in good health. His ballistocardiogram was unusually small in amplitude, -58%. He remained in good health until 1940 when he consulted me and gave a typical history of mild angina pectoris after unusual effort. At that time he had no difficulty climbing 2 flights of stairs if he did not rush. In 1941 attacks of severe breathlessness returned, whether of cardiac origin or a recrudescence of his old asthma cannot be stated with certainty. He was admitted to a hospital in another city but before a study could be made, fell or jumped from the window and was found dead on the pavement below. Necropsy was not performed because the subject, always interested in the medical profession although not a doctor, had willed his body to the Harvard Medical School for dissection; a fact I mention as a tribute to him.

*Subject K. V.* had always had excellent health and was 74 years old when examined in 1938. This ballistocardiogram, reproduced in Figure 1, was extremely small in amplitude, the measurements deviating from the normal young adult average by -60%.

She developed typical mild angina 4 years

later and has continued to suffer from such attacks. She is alive today, aged 83, her activity greatly limited by a severe arthritis of both knees which makes it impossible to say what her exercise tolerance would be. She has no attacks at rest.

*Subject D. G.*, a physician, was 63 when tested in 1939 and considered himself to be in the best of health. His ballistocardiogram is reproduced in Figure 1. The waves are abnormally small and J fails to dominate the record, not exceeding H in many complexes. I and J, though small, are normal in form, the calculation giving a deviation of -60% from the average of healthy young adults.

This subject suffered from an attack of typical coronary infarction in 1945 and was treated in the University Hospital. He made a good recovery but did not resume the practice of medicine. He now writes that at present he is careful of himself and takes no severe exertion. On this regimen he has had no angina, but he notices some undue dyspnea on mild exertion.

*Subject F. G.* was 59 years old when tested in 1937, and was leading a very strenuous life at that time, even for one of the medical profession. His ballistocardiogram was normal in form; it showed abnormally small deflections, the calculation being -58%. He had a typical attack of coronary infarction in 1939, and 2 minor episodes since that time may have been of the same nature. He made a good recovery, and at present, aged 70, seems to be working almost as hard as ever.

The other cases who developed heart disease, with one exception, gave ballistocardiograms with abnormally small deflections compared with the healthy young adults and also with the majority of their age group, but they do not stand conspicuously alone in Figure 2 as the cases mentioned above.

*Subject G. E.* was 74 years of age when tested in 1939. Three years before this date anemia had been discovered and a diagnosis of pernicious anemia (?) had been made. The anemia responded poorly to reticulogen and there was doubt as to the diagnosis. Slight pain suggestive of angina pectoris had occurred at this time but this had disap-

peared after his blood had slowly returned to normal. The diagnosis of angina pectoris was not made by the attending physician in 1936. When tested in 1939, G. E. considered himself to be in perfect health and his blood count was entirely normal. He was, however, taking liver extract. The record is reproduced in Figure 1, the calculation was  $-51\%$ .

Angina pectoris was first diagnosed in 1942. In October 1943 he had a severe attack of constant substernal pain and was admitted to the University Hospital where acute coronary occlusion was diagnosed. The electrocardiogram strongly suggested an acute infarction involving the posterior and possibly also the lateral surface of the left ventricle, with partial heart block. He went downhill steadily and died 6 weeks after the onset. There was no necropsy. Because of trouble anteceding the ballistocardiogram there is doubt whether this patient should be included in our series.

*Subject D. H.*, a physician, was 85 years old when tested in 1938. He was well preserved and insisted that his health was excellent. Indeed he came to the hospital only because of a laceration of the scalp. P. E. disclosed a rough systolic murmur, and arteriosclerosis of the palpable vessels. The electrocardiogram was normal. The heart was normal in size by Roentgen ray.

He was readmitted to the University Hospital in 1940. The heart was now slightly enlarged by Roentgen ray and the electrocardiogram showed diphasic T waves in Leads 1, 2, CF, and CF<sub>1</sub>. His prostate was moderately enlarged, B.P. 160/90, Roentgen ray of the chest showed emphysema. The cardiac murmurs were more prominent and arteriosclerotic heart disease was diagnosed. He did fairly well until the age of 92 when he developed a left hemiplegia and died several weeks later at the Philadelphia General Hospital. I can find no record of a necropsy.

*Subject N. E.* was 65 when tested in 1939, and considered himself in excellent health. His ballistocardiogram was normal in form but unduly small, the deviation being  $-40\%$ .

He continued in good health until 1946. Then, when at work in the laboratory he developed a precordial pain of moderate severity. He walked to the University Hospital and was admitted. Electrocardiogram next day indicated a posterior cardiac

infarct. He died suddenly the day after. Necropsy confirmed the diagnosis of acute posterior cardiac infarction; death was due to rupture through the infarct. Both coronaries showed many places where the lumen was greatly reduced.

*Subject H. B.*, an orderly, was first tested in 1937. This record and 3 subsequent ones were reproduced in a previous communication,<sup>5</sup> and I have little to add to the earlier after-history there recorded. The first record deviated from the average of healthy persons by  $-44\%$ . He suffered from a typical attack of posterior cardiac infarction in 1939 which was treated in the University Hospital. He recovered from the acute episode, but suffered from angina pectoris which increased in severity until he was forced to leave his job as hospital orderly in 1941. He could not be followed further.

*Subject I. G.* was 57 years old when tested in 1937, and was in excellent health. The ballistocardiogram was normal in form but unusually small; the calculation showed a deviation of  $-44\%$ .

The after-history of this case was completely given in the 5 year follow-up.<sup>4</sup> Angina pectoris was first diagnosed in 1942. His last illness began with pneumonia complicated by emphysema; while convalescing he died suddenly. Necropsy showed severe widespread arteriosclerosis of the coronary arteries and an infarct of the lateral wall of the left ventricle which was judged to be several days old.

*Subject K. V.* was 53 when tested in 1939; he gave a history of a transient attack of auricular fibrillation several years before, but he denied all other symptoms of cardiac disease. The record was normal in form and deviated from the average of healthy young adults by  $-37\%$ ; it is reproduced in Figure 1.

This subject developed angina pectoris after unusual effort; the onset was gradual and it is hard to date. He has continued to suffer from it but at present, aged 61, he is leading an active and useful life as a physician.

*Subject C. N.* was mentioned under the heading of abnormal records but we have included his data in Figure 2 because the abnormality did not affect the I and J waves used to estimate cardiac output. His record deviates by  $-41\%$  from the average of healthy young adults.

The subjects described above all had circulations believed to be abnormally small. The last case is the only exception. Although not so in absolute size, in terms of ideal weight, the deflections of this subject's ballistocardiogram were larger than those of anyone else in the same age group.

*Subject S. C.* was 44 years old when tested in 1937. Interpretation of this record is rendered difficult by the fact that the subject was unusually small, only 4'4" in height and 98 pounds in weight. Using our usual criteria the calculation deviates from the average of healthy young adults by +20%. There was a history of rheumatic fever in 1928 but no cardiac lesion had ever been demonstrated. The gall bladder was removed in 1936 for calculus cholecystitis; recovery from the operation was complete. However, in 1942 when hill climbing at high altitude in Colorado there was an attack of pain of brief duration "undoubtedly angina pectoris." The same year at Philadelphia there were 2 similar attacks after running to catch a bus. In 1944 a previously unrecognized chronic urinary tract infection was discovered and this required treatment. At present (1947) the subject can walk long distances without distress but is perhaps unusually short of breath on stair climbing. A physician especially interested in this case wonders whether this subject has more "heart disease" than the average person of the same age.

#### CASES WHO DIED WITHOUT DEVELOPING HEART DISEASE.

*Subject K. R.* was 65 when tested in 1939 and appeared in excellent health. His ballistocardiogram was larger than anyone else in his age group, deviating from the average of healthy young adults by -13% which placed him well within normal limits for that group. In 1941 he was admitted to the hospital because of gastro-intestinal symptoms. Laparotomy disclosed an inoperable carcinoma of the rectum. He died 4 months later of uremia after a period of anuria. Permission for necropsy was refused.

*Subject S. V.* was 61 when tested in 1939. A famous football player in his youth, he was in excellent health. His ballistocardiogram shown in Figure 2 was entirely normal. In size it was above the average of his age

group and -34% in relation to the average of healthy young adults.

This subject was in excellent health until the day of his death. In 1945 while attending to his medical duties he fell unconscious and died in a few minutes. The necropsy demonstrated a subarachnoid hemorrhage due to rupture of a small congenital aneurysm. The heart was normal.

*Subject H. T.* was 47 years old when tested in 1939. For many years he had taken alcoholic beverages in large amounts but he certainly considered himself to be in good health. His ballistocardiogram was normal in form but one of the smallest of his age group, and it deviated from the average of healthy young adults by -44%.

This subject remained in reasonably good health until 1945 when he first noted weakness, loss of weight and distention of the abdomen. Examination disclosed slight jaundice, a liver edge down to the umbilical level, and a doubtful mass in the left lower quadrant. Laparotomy disclosed cirrhosis of the liver with ascites. The gall bladder was distended so a cholecystostomy was done. He went down hill rapidly and died 7 days after the operation. Necropsy showed a typical Laennec's cirrhosis with ascites, fibrocaseous tuberculosis of the lungs both active and inactive, and 2 ulcers in the terminal ileum. The heart was normal.

*Subject N. O.* was 48 when she was tested in 1938. Her record was normal in form and but little below the mean of her age group in size. It deviated from the average of normal young adults by -34%.

This subject remained in good health until a few months before her death in 1940. After becoming acutely ill she entered the University Hospital. The Roentgen ray disclosed widespread lesions of both lungs judged to be due to metastatic malignancy. She soon developed hemiplegia and died. There was no necropsy.

*Subject X. R.* was 72 when tested in 1938. In his youth he had been a famous athlete, holding a world's record, and he had always kept himself in top physical condition by vigorous regular exercise. He suffered occasionally from asthmatic attacks during the pollen season. A blood pressure of 170/100 was found and judged to be due to tenseness. The ballistocardiogram was normal in form and above the average of his age group in

size. Indeed it was well within the normal limits of the healthy young adults.

About 2 years before his death in 1942 he developed symptoms of prostatic obstruction but he refused both surgical treatment and medical supervision until near his end. He died of urinary tract infection and uremia in another hospital. There was no necropsy.

**CONCERNING A CASE WHO REMAINED WELL DESPITE ADVANCED AGE.** Just as interesting as the after-histories of those who fell ill is that of Subject M. R., who was 79 at the time of the test in 1939. He considered himself in excellent health then and his ballistocardiogram is reproduced in Figure 1. Normal in every way its size places it near the top of his age group and not far from the average normal of healthy young adults.

Consistent with this surprisingly normal record at such an advanced age, this subject is alive and well today, aged 87, and seems as active as he ever was.

**Discussion.** Inspection of the records shown in Figure 1 shows the main feature which I wish to emphasize. The patients whose records were abnormal in form, or abnormally small in amplitude, developed heart disease in large numbers during the decade following.

Measurements of these records confirm the impression gained by inspection, although there is some doubt as to how the figures obtained by measurement can best be applied to the detection of abnormality. Our data were first used to calculate cardiac output according to our original "area" formula,<sup>4</sup> and the results expressed this way were given in a preliminary report.<sup>6</sup> When compared in this way the subjects who eventually developed serious cardiac difficulty were found to have had cardiac outputs low in relation to subjects of the same age group, and even lower in relation to healthy young adults. But the use of the factor representing aortic diameter, present in our old formula,<sup>5</sup> seems no longer justified in a calculation of cardiac output.<sup>7</sup> Therefore in calculating the data recorded in Figure 2 it was omitted. By so doing the

decline in amplitude of ballistocardiograms as age advances is more clearly shown; a finding consistent with the diminution of cardiac output as age advances suggested by the data of Cournand *et al.*<sup>1</sup> By this method of calculation the abnormalities of those who eventually developed heart trouble are emphasized even more.

Another uncertainty is how the measurements of the ballistic record should be related to body size. In Figure 2 we have calculated the results in terms of both actual and ideal weight, the latter derived from age, sex and height in accordance with actuarial tables.<sup>2</sup> The second method reduces the scatter of the data. Inspection of Figure 2 demonstrates that the cases eventually developing heart disease gave conspicuously low values when either actual or ideal weight was employed.

It is indeed striking that each of the 6 cases giving records whose amplitude, referred to actual weight, differed from the average of healthy young adults by more than 52% developed coronary heart disease within 10 years. When ideal weight is employed, this is true of only the 4 lowest cases; but a line drawn at a level of -44% below the mean of healthy young adults divides the data so that 50% of the cases below developed heart disease, in contrast to but 5% of those above; a highly significant difference.

There is, however, 1 case which is a conspicuous exception to the generalization; that those fated to develop heart disease have abnormally small impacts before their disease becomes manifest. In the 40-49 age group is 1 subject (S. C.) who showed a record far larger than the others in this group, but who has had 3 attacks which may well have been angina on most unusual exertion. I make no pretense of having a completely satisfactory explanation of a finding so far from my expectations, but several thoughts come to mind. In 2 well-known conditions, hyperthyroidism and abnormal arterio-venous communications, a prolonged period of increased circulation often leads to serious cardiac abnormality. This patient



certainly did not suffer from either of these conditions, but one may wonder whether some other unknown condition, causing the hyperkinemia demonstrated in 1938, may not have been leading to cardiac abnormality in similar fashion. Perhaps more to the point is the unusual size of this subject who was only 4'4" tall; a factor which of itself raises doubt whether the data should be compared with those obtained in the series of more well-developed persons. But as I have reported other instances of patients with normal ballistocardiograms before and after an attack of coronary occlusion,<sup>5</sup> it seems evident that exceptions are to be expected. The point is, that if the ballistocardiogram is normal, the chances of developing coronary heart disease are much diminished.

Of equal interest is the after-history of a very active old man of 79 whose ballistocardiogram in 1939 was similar to that of the average healthy young adult. Apparently he had indeed the spirit of youth within him for today at 87 he seems as active and as healthy as ever.

**Summary.** Eight-to-10 year after-histories have been secured on 90 supposedly healthy persons over 40 years of age tested on the ballistocardiogram during 1937, 1938 and 1939 for the purpose of compiling normal standards.

Four of these subjects had ballistocardiograms abnormal in form. Three of the

4 developed coronary heart disease in the years which followed.

In 86 subjects the ballistocardiograms were normal in form. These results have been arranged according to the size of the ballistocardiogram as related to actual and ideal weight. The 6 cases giving the smallest records in proportion to actual weight developed coronary heart disease.

A line can be drawn through the data at a level 44% below the average of healthy young adults referred to ideal weight. Of these cases, 50% falling below the line developed serious heart disease, in contrast to 5% of those above; a highly significant difference.

Five subjects who gave ballistocardiograms normal in form and amplitude during the years 1937, 1938 and 1939 died within the next 8 to 10 years. None of them developed clinical evidence of heart disease, and in 2 the heart was normal at necropsy.

A man of 79 gave a ballistocardiogram whose amplitude was above that of most others in his age group and indeed equal to that of many young adults. He is now well and active at the age of 87.

A ballistocardiogram abnormal in form, or of unusually small amplitude is of serious prognostic significance.

The ballistocardiographic method gives promise of identifying coronary heart disease far earlier in its course than has been possible hitherto.

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## HYDROTHORAX IN CONGESTIVE HEART FAILURE

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FOR years our interest, like that of other physicians dealing with many cases of congestive heart failure, has been attracted by the preponderance of right hydrothorax in such patients. The problem of its mechanism has been difficult to solve and there has also been some difference of experience concerning the relative incidence of right, left and bilateral hydrothorax in congestive heart failure. Stimulated by recent papers on the subject, particularly by that of Bedford and Lovibond,<sup>1</sup> which has differed somewhat from our own experience, we have reviewed 100 cases of hydrothorax in congestive heart failure encountered at autopsy at the Massachusetts General Hospital during the past 10 years and are reporting that analysis herewith.

The literature on the subject has been reviewed by Bedford and Lovibond in their recent article. These authors analyzed 346 cases of congestive failure of which 136 showed hydrothorax as determined mostly by Roentgen ray examination (89 cases) and by paracentesis or necropsy in 20 of the remaining 47 cases. Hydrothorax was found in 45 of 109 necropsies. Of the 136 clinically studied cases, 68 had right hydrothorax, 42 left and 26 bilateral, thus showing a preponderance of right to left hydrothorax except in the cases of hypertensive heart disease with normal rhythm in which the ratio was reversed (left:right::19:10). In their series of 45 cases studied postmortem, right hydrothorax was found 11 times, left 9 and bilateral 25.

Bedford and Lovibond have emphasized the importance of the pulmonary circulatory venous drainage as well as of the systemic in the development of hydrothorax.

**THE PRESENT SERIES.** We have studied the autopsy and clinical records of 100 unselected cases of congestive heart failure with hydrothorax that died at the Massachusetts General Hospital from 1933 to 1941 in order to determine the relative incidence of right- and left-sided effusion *in toto* and according to the types of heart disease and the primary strains (that is, left ventricular and right ventricular) involved. It is essential to base such a study on postmortem data, not only for greater certainty as to the type of heart disease and the heart chamber chiefly affected, and to establish more accurately the presence, character and amount of pleural fluid on both sides, but to ascertain the vitally important facts concerning adhesions or even obliteration of either pleural cavity and the possible presence of pulmonary infarcts, conditions that are difficult or impossible to diagnose clinically, even with the help of the Roentgen ray. It is true that such a study does not take into account the early or mild cases of congestive heart failure but such cases rarely show hydrothorax anyway, and the bulk of the serious cases are presented in the autopsy series.

*Sex and Age.* Of the 100 cases, 77 were male and 23 were female. Their ages varied as follows: 0 to 11 years, 1; 11 to 20 years, 7; 21 to 30 years, 6; 31 to 40 years, 15; 41 to 50 years, 15; 51 to 60 years, 17; 61 to 70 years, 24; 71 to 80 years, 13; 81 to 90 years, 2.

The amount of fluid varied from 100 to 2000 cc. on a side, averaging about 500 to 600.

The character of the fluid was that of a transudate, occasionally blood stained, in 2 instances grossly bloody, and in 1 case

purulent on one side (due to a complicating infection) but clear on the other side.

The *side of the hydrothorax*: Unilateral right hydrothorax was more common than left in the ratio of 15 cases to 13 and it is of considerable interest that each of the 13 cases of unilateral left hydrothorax had an important factor in addition to the congestive heart failure, 12 of the cases showing complete obliteration of the right pleural cavity and the 13th infarction of the left lung alone. Only 2 of the 15 cases with unilateral right pleural effusion had an obliterated left pleural cavity, and only 2 others had unilateral right pulmonary infarction. The remaining 72 cases had bilateral pleural effusions, equal in almost half (34 cases), but in the other 38 cases much more preponderant on the right side than on the left in the ratio of 30 cases to 8.

The *etiologic types of heart disease*:

*Rheumatic heart disease* was more commonly encountered than any other type, being found in 34 cases, alone in 32 and complicated in 2 others (in 1 with hypertensive heart disease and in the other with coronary heart disease). Of the 32 uncomplicated cases, 28 had mitral stenosis with or without other valve lesions; only 3 cases had predominantly aortic valve disease. Of the 32 cases, 5 had unilateral right and 3 others unilateral left hydrothorax, the latter showing in 2 cases an obliterated right pleural cavity and in the other left sided pulmonary infarction. The effusion was bilateral in the other 24 cases, equal on the 2 sides in 9, greater on the right in 9 and greater on the left in 6 (1 of these had a solitary left pulmonary infarct). The other 2 cases of rheumatic heart disease showed bilateral hydrothorax, preponderant on the right in the hypertensive patient and equal on the 2 sides in the patient with coronary occlusion.

There were 28 *hypertensive cases*, uncomplicated in 14 and associated with coronary heart disease in 12, with rheumatic heart disease in 1 (cited above), and with cardiovascular syphilis in 1. Of the

14 uncomplicated cases, 3 showed unilateral right hydrothorax and 4 showed unilateral left hydrothorax, those 4 all revealing obliterated right pleural cavities. The other 7 cases had bilateral effusion, equal on the 2 sides in 2 but greater on the right than on the left in 4 of the remaining 5 cases. The 12 cases of hypertensive and coronary heart disease showed unilateral right hydrothorax in 2, unilateral left in 1 with an oblitative pleuritis on the right, and bilateral effusion in the other 9 (equal in 7 and preponderant on the right side in 2). The case complicated by syphilitic cardiovascular disease had bilateral effusion, greater on the right than on the left, and also bilateral pulmonary infarction.

*Coronary heart disease* was the type without complications in 21, 4 of whom showed unilateral right hydrothorax and 2 unilateral left (both cases having obliterated right pleural cavities). The other 15 had bilateral effusions, equal on the 2 sides in 7, greater on the right in 7, and greater on the left in the remaining patient. The 12 cases of coronary and hypertensive heart disease have been referred to in the preceding paragraph. The 1 case of coronary heart disease complicated by rheumatic heart disease, cited above, had equal effusions on the 2 sides.

*Aortic stenosis of the calcareous types* was present in 8 patients. There was a bilateral effusion in 7, 5 of whom showed more fluid on the right side than on the left, the sixth case showing equal effusions on the 2 sides, and the seventh more on the left than on the right. The eighth patient had a unilateral left hydrothorax due apparently to the combination of congestive heart failure and obliteration of the right pleural cavity.

One case with uncomplicated *cardiovascular syphilis* and congestive heart failure showed bilateral hydrothorax greater on the right than on the left, as did also the other syphilitic case, already mentioned, complicated by hypertension.

*Chronic constrictive pericarditis* was the factor in 2 cases of congestion. In 1 case

the hydrothorax was right-sided with an obliterated left pleural cavity and the other case showed the opposite picture, a left-sided effusion with an obliterated right pleural cavity.

A single example of *cor pulmonale* showed a pure left-sided effusion with right-sided oblitative pleurisy.

Out of the 100 cases surveyed, only 1 was due to *congenital heart disease* (*cor batriatum triloculare*) and this exhibited a bilaterally equal hydrothorax.

The final group represents 5 cases of cardiac enlargement and failure of *unknown cause*. All had bilateral hydrothorax, 3 equal in amount and 2 predominantly right-sided. Pulmonary infarcts were present in 3 cases, right-sided in 1 with predominantly right-sided effusion, and multiple in the other 2, 1 with chiefly right-sided and 1 with equal amounts of pleural fluid.

*Type of heart failure:* An attempt was made to determine the incidence of left, right and bilateral heart failure. Certainly the majority started as unilateral left strain: 14 hypertensive cases, 12 hypertensive and coronary, 1 hypertensive and syphilitic (with aortic regurgitation), 21 coronary and 12 others with aortic valve disease (stenosis or regurgitation or both), a total of 60, and yet these as noted above showed a slight preponderance of right hydrothorax (31 cases), both unilateral (right 9 and left 8, all of the latter showing also obliteration of the right pleural cavity) and a greater amount when bilateral (right 22, left 3 and equal 18). Of the 29 cases of preponderant mitral stenosis and hence primarily right ventricular strain, 12 showed either right or predominantly right-sided effusion, and 9 were predominantly left. Of the 3 of these which had unilateral left-sided effusions, 2 had oblitative pleuritis on the right side and the remaining case showed left-sided pulmonary infarction. Among the other 6 cases with bilateral and chiefly left-sided effusion, 1 presented a left-sided pulmonary infarction. The remaining 8 cases had bilateral equal

effusions. The other case of right-sided strain, a case of *cor pulmonale* secondary to pulmonary endarteritis had a small left-sided effusion but also had oblitative adhesions on the right. The remaining 10 cases of the 100 had primary strain on both ventricles, 5 of these showed equal effusions on the 2 sides, 3 showed more fluid on the right than on the left, 1 showed fluid only on the right, and 1 only on the left, explainable probably by obliteration of the opposite pleural cavity in each of the last 2 cases.

At the time of death 73 of the 100 cases showed total heart failure, 14 apparently unilateral right, and 12 apparently unilateral left; the 100th case showed systemic congestion due to chronic constrictive pericarditis.

It is also worthwhile to call attention to the frequency of pulmonary infarction in this series of 100 cases of congestive heart failure; 30 patients (30%) showed such involvement, 15 or one-half on both sides, 11 in the right lung alone, and 4 in the left alone. Of the 15 cases with bilateral infarction, 11 showed bilateral pleural effusions, with equal amounts in 5 of them and preponderant right hydrothorax in the other 6. Of the 11 cases with right lung infarction alone, 2 had unilateral right pleural effusion and 9 bilateral effusion (equal in 3 and with preponderance on the right in the other 6). Of the 30 cases showing pulmonary infarctions, 26 had right-sided or multiple infarcts, and 16 of these showed either right-sided or predominantly right-sided effusions, and none showed left-sided and only 1 a predominantly left-sided effusion. Of the 4 cases showing left-sided infarcts only 2 had bilateral effusions, 1 equal and 1 predominantly left-sided, and 2 had left unilateral effusions, 1 possibly due to an oblitative right pleuritis.

In this series 67 cases had electrocardiograms. Eleven cases are omitted because of oblitative pleurisy on the side opposite the effusion or because of pulmonary infarction on the same side as the effusion. Of the remaining 56 cases, 17 showed

auricular fibrillation with 9 or half having right- or predominantly right-sided effusions. Among the 38 cases having regular rhythm, 27 or more than half showed right-sided or predominantly right-sided effusions. One case had complete heart block with bilateral effusion. The cases are further divided into those showing right, left and total strain. The 15 cases of rheumatic heart disease represent those showing right strain. Eight of these showed auricular fibrillation and 7 had regular rhythm. In the cases with auricular fibrillation, 3 had right or predominantly right effusion, while among the cases with normal rhythm, 4 cases had right or predominantly right effusion. The 28 cases of coronary, hypertensive and aortic valvular disease are grouped together under left ventricular strain. Of the 7 cases having auricular fibrillation, 4 cases showed chiefly right-sided effusion, while of the 21 cases with regular rhythm, 14 cases showed largely right-sided effusion. Thus in this small series of cases, neither the rhythm itself, nor the rhythm combined with the type of heart strain, exhibits any correlation with the location of the pleural effusion.

Another series of 100 cases of left ventricular failure were studied in relation to hydrothorax. In all cases, the diagnosis of hydrothorax was confirmed by Roentgen ray. The patients entered the Massachusetts General Hospital between the years 1937-1945. Patients who entered because of left ventricular failure (acute pulmonary edema and dyspnea) were primarily used in this series. In addition, other cases with primary left ventricular strain (such as hypertensive heart disease or aortic valvular disease)—some of whom exhibited signs of right failure later in the course of the disease—were included. However, no cases of rheumatic heart disease or primary right ventricular strain were used. Cases with known recent pulmonary embolus were automatically excluded because of the demonstrated possible relation of pulmonary embolus to hydrothorax in our autopsy cases. In

this series of 100 cases with left ventricular failure, 76 showed no hydrothorax, 16 showed bilateral hydrothorax (1 of which was predominantly right-sided, the remainder were equal). Six had unilateral right hydrothorax and 2 had unilateral left hydrothorax. Six of the 24 cases which had hydrothorax had no associated signs of right heart failure, such as enlarged liver or ankle edema; 18 did develop such signs secondarily.

It is of interest that the Roentgen ray report of 1 of the cases of unilateral left hydrothorax stated that there was "thickening of the lower pleura on the right." This finding is similar to the finding (in our series of autopsy cases) of obliterative pleurisy on the right in cases with unilateral left hydrothorax.

Also of note is the fact that 2 of our cases (included under bilateral hydrothorax) were found to have unilateral left hydrothorax on Roentgen ray films taken after treatment. Thus, these 2 cases might have been classified as unilateral left hydrothorax if earlier roentgenograms had not been on the record. It is not unlikely that some of the cases of unilateral right hydrothorax may have previously had bilateral hydrothorax, but our records do not show this possibility.

Finally, it is of some interest that 14 of the 100 cases had obliterating pleural adhesions (12 on the right and 2 on the left). Three more cases had extensive pleuritis (2 on the right and 1 on the left). Thus in this small series of cases both hydrothorax and important pleural adhesions were preponderantly right-sided.

**Discussion.** This analysis has confirmed the clinical impression of many years and the published findings of most observers of the preponderance of right-sided hydrothorax over left in congestive heart failure, no matter what the pathogenesis of pleural effusions of cardiac origin may be. This preponderance was present in our cases without regard to the type of heart disease or the side of the heart under initial major strain.

Furthermore, it is of interest that left unilateral hydrothorax in our cases was always accompanied by an adequate explanation in addition to the congestive heart failure, consisting of complete obliteration of the opposite pleural cavity in all but 1 case in which there was infarction of the lung on the same side. This was not true of the majority of the cases of right unilateral hydrothorax.

The explanation of the preponderance of right hydrothorax in congestive heart failure remains obscure but quite possible factors include the larger extent of the circulation of right lung and pleural surfaces on the right side than on the left and the greater frequency of right-sided as compared with left-sided decubitus.

**Summary.** 1. We have analyzed 100 cases of congestive heart failure showing hydrothorax at autopsy at the Massachusetts General Hospital.

2. Fifteen cases showed unilateral right hydrothorax, 13 showed unilateral left hydrothorax. Each one of the latter revealed an important factor in addition to the congestive failure, there being found complete obliteration of the right pleural cavity in 12 and unilateral left pulmonary infarction in the remaining case, in contrast to only 4 such explanations among

the 15 cases of unilateral right hydrothorax.

3. The remaining 72 cases showed bilateral pleural effusions, equal in 31 but preponderantly right-sided in 32 of the remaining 41.

4. The etiologic type of heart disease and the side of the preponderant initial ventricular strain (left *vs.* right) made little difference as to the location of the hydrothorax, but the great majority of these cases at autopsy showed right heart failure usually superimposed on left.

An additional 100 cases of acute left ventricular failure in hypertension or aortic valve disease were analyzed as to the subsequent occurrence of hydrothorax during the next few weeks; 76 of the 100 showed none, while 16 developed bilateral hydrothorax, 6 unilateral right and only 2 unilateral left; of the 24 cases who developed hydrothorax, only 6 failed to show any recognized sign of right heart failure and it is possible that the venous pressure might, if recorded, have been elevated in those 6 cases also.

5. Pulmonary infarction (superimposed on or precipitating or aggravating the congestive failure) was found in 30 cases and played a secondary rôle in the localization of the hydrothorax.

**Addendum.** After completing this paper an article by Edgar M. McPeak and Samuel A. Levine, entitled "The Preponderance of Right Hydrothorax in Congestive Heart Failure," appeared in the December 1946 number of the *Annals of Internal Medicine*, vol. 25, p. 916. The conclusions of these authors in general correspond to our own with minor differences. The combination of these series of cases in Boston should help very much to clarify the clinical features of hydrothorax in congestive heart failure.

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## ATRIAL SEPTAL DEFECT

### CORRELATION OF AUTOPSY FINDINGS WITH DATA OBTAINED BY RIGHT HEART CATHETERIZATION

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At Emory Medical School the method of heart catheterization has been used more than 1500 times. Of patients so studied, only 1 case of atrial septal defect has come to autopsy. The literature has revealed no other case report of congenital cardiac defect which had both heart catheter studies and autopsy. The following case is presented to illustrate the value of heart catheterization in diagnosis of atrial septal defects.

**Case Report.** Mr. T. F. S., a 37 year old school teacher, was Case 8 in the series of atrial septal defects studied by Brannon, Weens and Warren,<sup>1</sup> who give the complete case report. In brief, the patient had been diagnosed as a case of congenital heart disease with myocardial failure and compensatory polycythemia. The right heart catheterizations revealed that: 1. The oxygen content of the right atrial blood was distinctly higher than the superior vena caval blood.

2. The oxygen content of the right atrial and right ventricular blood was the same.

3. The right ventricular (pulmonary artery) pressure was extremely high (140 mm. Hg), the maximum normal is 40 mm. Hg.

4. Pressure in the right atrium was elevated.

5. Calculated left ventricular output was roughly normal. Right ventricular output was at least twice this.

These data could have been obtained only by heart catheterization. They helped clarify the diagnosis of atrial septal defect and made the diagnosis of pulmonary vascular hypertension.

**Course.** After these studies, the patient found that inhalations of oxygen by mask improved his comfort only slightly, in spite of the fact that blood studies had revealed increased saturation of the arterial blood after oxygen inhalation. His course was

gradually downhill over the next 8 months. Mercurial diuretics were frequently used and occasionally venesection was done. The edema and polycythemia both increased. He was confined to bed almost constantly. His last hospital admission started March 1946. At this time, auricular fibrillation existed. He lost 20 pounds in a month of intensive diuresis, but his polycythemia and hemoconcentration simultaneously increased and he died after a series of painful pulmonary infarcts which persisted over a period of 3 weeks.

**Autopsy.** The major anatomic diagnoses are listed: 1. Interatrial septal defect, congenital (septum primum defect).

2. Dilatation and hypertrophy of heart, predominantly right-sided, marked (640 gm.)

3. Dilatation of tricuspid and pulmonic orifices, marked.

4. Separation of cusps of mitral and of tricuspid valves.

5. Fibrosis of mitral and tricuspid valves.

6. Dilatation of pulmonary artery and branches.

7. Pulmonary arteriosclerosis.

8. Arteriosclerosis, generalized and coronary, moderate.

9. Thrombosis of many branches of pulmonary artery, bilateral, with pulmonary infarcts, multiple.

10. Chronic passive congestion of viscera.

Description of the heart and lungs follows; details of other anatomic structures are deleted for brevity. All of the chambers of the heart are enlarged, especially the right auricle and right ventricle. The ductus arteriosus is not patent. There is a circular defect in the lower portion of the interatrial septum that is 5 cm. in diameter. The foramen ovale is closed and the limbus fossæ ovalis is easily seen. The valves measure: tricuspid valve 17.5 cm., pulmonic valve 10 cm., mitral valve 11 cm., aortic valve 6 cm. The cusps of the tricuspid valve are thickened, but are smooth except for slight

irregularity at their free margins. The cusps do not meet at the commissures, leaving a defect of approximately 0.5 cm. The papillary muscles are tremendously enlarged. The pulmonic valve shows only slight thick-

ening of the cusps with some loss of the normal translucency. The mitral valve, like the tricuspid, is thickened and its commissures do not meet. The cusps are smooth with very slight nodulation. The aortic

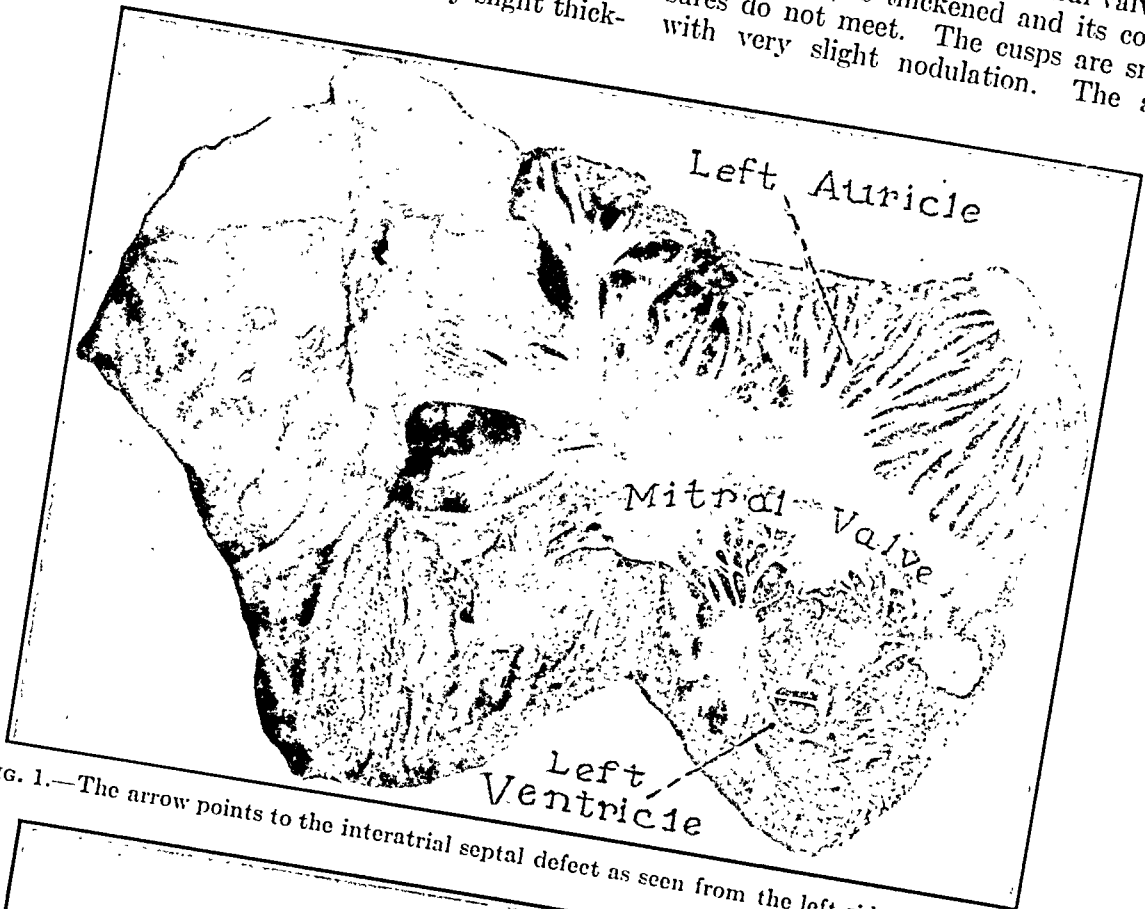


FIG. 1.—The arrow points to the interatrial septal defect as seen from the left side of the heart.

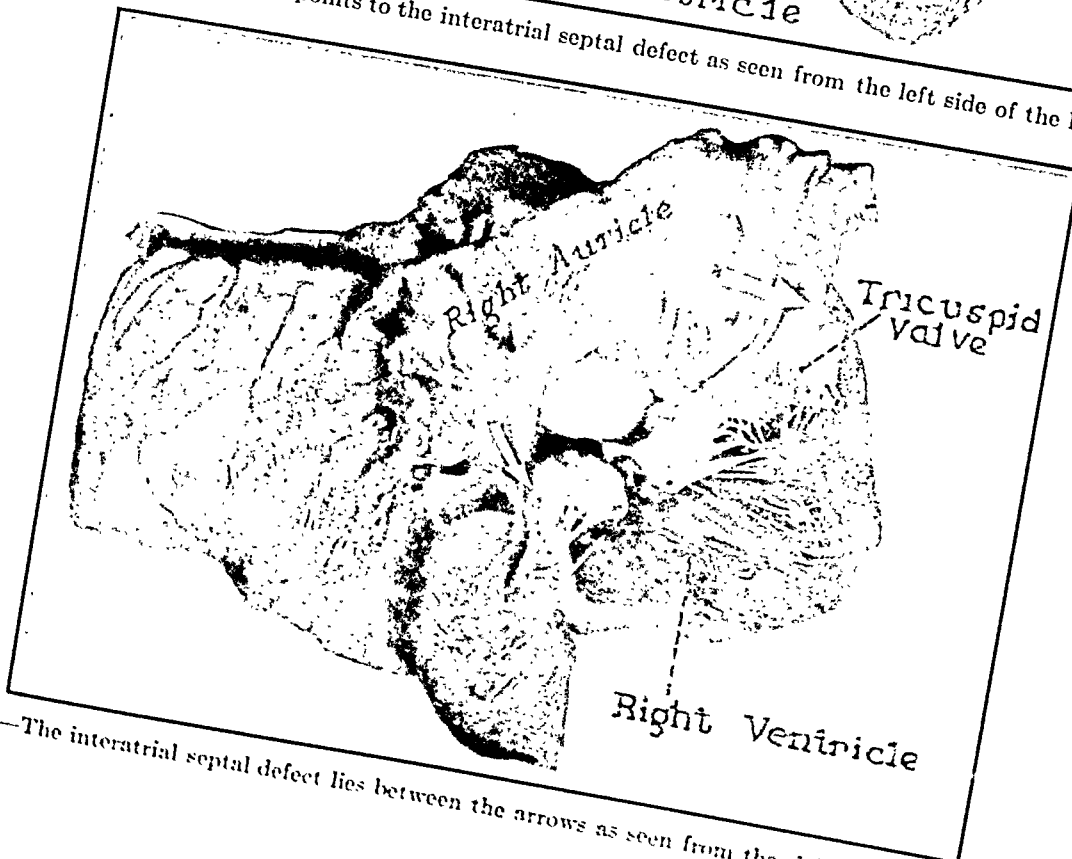


FIG. 2.—The interatrial septal defect lies between the arrows as seen from the right side of the heart.



valve has a few atheromatous deposits, but shows no gross abnormalities. There are numerous atheromatous deposits about the root of the aorta. The myocardium is firm and of a deep red color. The left ventricular wall is 2 cm. thick near the coronary sulci and tapers towards the apex, measuring 0.6 cm. at the apex. The right ventricular wall averages 1.6 cm. in thickness. The wall of the right atrium is thickened and at one point measures 1.2 cm. though the average thickness is approximately 0.4 cm. The coronary vessels are patent, but there is moderately severe atherosclerosis.

There are scattered atheromatous deposits throughout the aorta, which seems abnormally small in relation to the pulmonary arteries.

The surface of the lungs is normal except for irregular, dark red areas over the lower portion of the left upper lobe and over the right middle and lower lobes.

The pulmonary arteries in the region of the hilum are approximately twice their normal size. Dissection reveals firmly adherent blood clots occluding the large branch to the lower portion of the left upper lobe and the branches to the right lower and middle lobes. The veins are not remarkable. The bronchi are red and contain only a small amount of secretion.

The cut surface of the left lung is normal except that the lower portion of the left upper lobe is dark red and firm. In the lateral portion of this area there is a large vessel (diameter 0.5 cm.) filled with partially organized blood clot. The right lung shows similar changes. The large vessels to its lower and middle lobes are occluded by firmly adherent blood clot. There are reddish firm areas in the lower lobe and the middle lobe and the fissure between the lower and middle lobes is partially obliterated by fibrous adhesion.

Microscopic lung sections reveal patchy edema and slight emphysema in areas of lung surrounding the infarcted areas which are intensely congested and edematous. All vessels are sclerotic, thickened, and markedly dilated. In the infarcted areas vessels contain organizing thrombi. Fibrous and fibrinous pleuritis is present.

**Discussion.** The usefulness of right heart catheterization in the diagnosis in this case was in the demonstration of the

increased oxygen saturation of right atrial blood as compared to vena caval blood, and in the demonstration of the increase in right ventricular pressure. In addition, pertinent data relative to factors influencing ventricular output were obtained.

In only 2 conditions can the right atrial blood oxygen saturation exceed the vena caval blood oxygen saturation—in interatrial septal defect, with the flow of oxygenated blood from left to right atrium, and in the case of aberrant pulmonary veins which empty into the right atrium bringing blood of greater oxygen saturation than that which comes from the vena cava. The latter situation is rarer than interatrial septal defect and is not associated with as much cardiac enlargement.

Increase in right ventricular pressure can be surely demonstrated in no other way than by right heart catheterization. In itself it suggests pulmonic valve stenosis, pulmonary vascular stenosis or disease of the type found here, *cor pulmonale* due to whatever cause, or interventricular septal defect. Correlation of the pressure reading with the physical and Roentgen ray findings is necessary to clarify the diagnosis.

The right ventricular output in this case was shown to be roughly twice that of the left ventricle. Yet the right atrial pressure was necessarily less than the left, since the flow of blood through the atrial septal defect was from left to right. This is at variance with the old teaching of Starling that the ventricular output rises with increase in atrial pressure, and points to the necessity of consideration of other factors which may influence ventricular output.

The problem of the maintenance of cardiac compensation in the management of this case was complicated by the presence of pulmonary vascular disease and pulmonary vascular thrombi. In a congenital cardiac defect such as an interatrial septal defect, polycythemia may develop in a salutary manner, increasing the oxygen carrying capacity of the blood by increasing the volume of circulating

hemoglobin. Up to a certain point, this was desirable in this case, but beyond this point, increase in the hematocrit value tended to increase the viscosity of the blood, thereby increasing the load on the heart and the tendency to thrombus formation in the vessels, particularly in such vessels as might be diseased or damaged, as in the pulmonary circulation. Similarly in the use of diuresis to relieve edema of the tissues, it was desirable to find the point at which mechanical stress would be lessened by removal of fluid without dehydrating to the point of concentrating the blood, increasing its viscosity and predisposing to thrombus formation.

The data obtained by right heart catheterization, namely the increase in ventricular pressure and the increased saturation of the arterial blood with oxygen inhalation, showed the presence of pul-

monary vascular obstruction. This at once showed the importance of keeping the viscosity of the blood below a point tending to thrombus formation. It was thought that venesection was more feasible and less expensive than the continued use of heparin and definitely less dangerous than the use of dicoumarol.

In the final stages of the patient's illness, the elimination of edema and restoration of cardiac compensation proved less of a problem than the prevention of pulmonary thrombi and infarction. The terminal events were a series of pulmonary infarcts.

**Summary.** 1. A case of interatrial septal defect and pulmonary vascular disease was studied by the method of right heart catheterization.

2. The data obtained are given and discussed in the light of autopsy findings.

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## A CASE OF FATAL ARTERIAL OCCLUSIONS DUE TO ANEURYSM OF THE ABDOMINAL AORTA

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As long ago as 1906 Nixon<sup>3</sup> wrote: "Ever since Beatty gave his inimitable description of a case of abdominal aneurysm simulating stricture of the rectum in a man 33 years old, the vagaries of this disease have been closely studied and discussed; still the malady provides fresh combinations of signs and symptoms to puzzle and baffle clinicians." Forty years later we still find new and confusing syndromes in cases of abdominal aortic aneurysm. A tabetic patient, recently admitted to this hospital, presented symptoms of abdominal aortic aneurysm with scrotal gangrene and was found to have occlusion of the inferior mesenteric and hypogastric arteries. A search of the literature failed to reveal a similar case.

**Case Report.** A 66 year old, white, unemployed clerk was admitted on Aug. 4, 1946, complaining of a "burn" of his scrotum and perineum following exposure to a heating pad. For the preceding 10 years he had been disabled because of symptoms of tabes dorsalis, first diagnosed in 1937 at another hospital. At that time he was found to have: staggering gait, positive Romberg sign, Argyll Robertson pupils, beginning optic atrophy, absent patella and Achilles reflexes, and loss of vibratory sensation in both legs. Repeated Wassermann tests of blood and spinal fluid were positive. Although intramuscular injections of bismuth were given, he had, during the last few years, lost 40 pounds and developed difficulty in voiding, constipation and diminution of vision. On Aug. 2, 2 days before admission, he applied an electric heating pad to his perineum for relief of dysuria. He fell asleep, and awoke in a few hours with swelling, redness and blistering of the perineum. During the next 24 hours crampy pains began in the lower abdomen and back.

On admission the patient was extremely weak and complained of mild, generalized abdominal pain. His temperature, pulse and respiration were normal. The blood pressure was 115/75 in both arms. The penis was normal. The scrotum was bluish purple, edematous and cool; over its anterior surface were several small vesicles containing cloudy fluid. The perineum and gluteal regions, and to a lesser extent the inner thighs, were erythematous and edematous. Examination of the eyes revealed Argyll Robertson pupils, advanced optic atrophy and arteriosclerotic changes. The abdomen, except for slight distention, was normal. Vibratory and position sense were lost in both legs.

**Laboratory Observations.** Hemoglobin, 15 gm.; leukocyte count, 10,500; blood urea nitrogen, 55 mg. per 100 cc.; serum protein, 5.1 gm. per 100 cc. The blood Kolmer and Kline tests for syphilis were negative.

**Course in Hospital.** On admission he did not appear acutely ill. Because of the inflammatory signs, 50,000 units of penicillin were given intramuscularly every 4 hours. The abdominal pain suggested tabetic crisis, and prostigmine was given for symptomatic relief. During the 12 hours after admission the patient gradually became disoriented. Eighteen hours following admission, he suddenly stopped breathing and became pulseless. After artificial respiration, plasma infusion, and oxygen by nasal catheter, the pulse returned and consciousness was slowly regained. The blood pressure slowly rose to 80/50. In the next few hours definite gangrene of the scrotum and perineum developed (Fig. 1). The peripheral pulses, however, remained palpable in both legs. The abdomen became distended, rigid and tender. In spite of intravenous fluid therapy and continued oxygen, the blood pressure gradually fell. Death occurred 26 hours after admission.

*Significant Findings at Autopsy.* (No. 46-427, performed 4 hours after death by Dr. Robert F. Conant.) *External genitalia:* the scrotum and perineum were gangrenous. The skin and subcutaneum showed necrosis with hemosiderin deposition and cellular infiltration. *Gastro-intestinal tract:* the

descending colon, sigmoid and rectum were gangrenous; the bowel wall was necrotic and edematous, containing red blood cells, neutrophils and macrophages. *Heart:* the anterior wall of the left ventricle was fibrotic with severe narrowing of the anterior descending coronary by atherosclerosis. *Aorta:*



FIG. 1.—Scrotal gangrene (20 hours after admission).

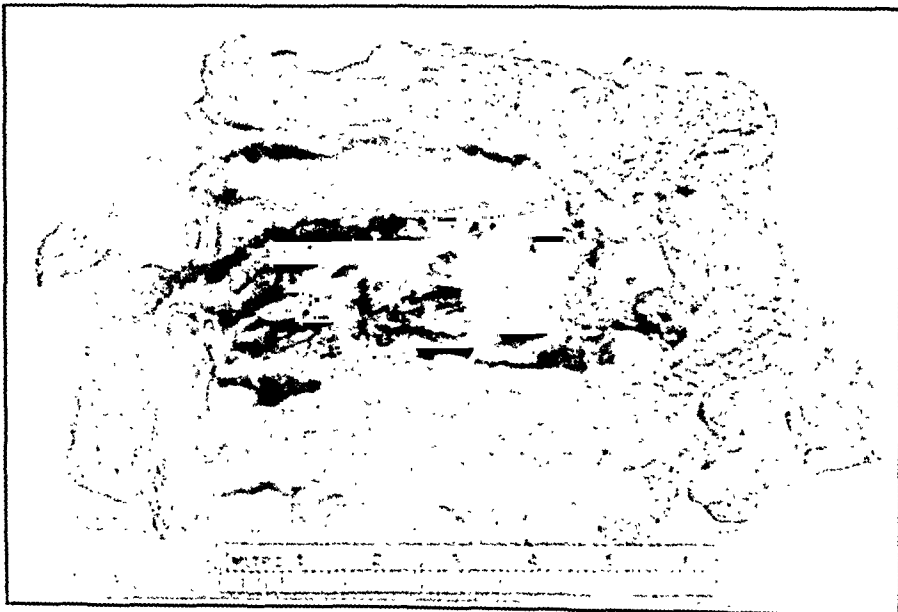


FIG. 2.—Specimen showing the aneurysm of the abdominal aorta.

the thoracic aorta showed scattered intimal plaques and moderate lymphocytic infiltration; the plaques increased in number distally with several areas of ulceration and subintimal hemorrhage. Just above the bifurcation there was a saccular aneurysm 4 x 5 x 3 cm., extending almost to the inferior mesenteric artery (Fig. 2). It contained a laminated thrombus, a small portion of which was lying free and was occluding the ostium of the inferior mesenteric artery. A dislodged bit of the thrombus had completely occluded the mouth of the right hypogastric artery. Microscopic examination showed that the thrombus in the aortic aneurysm was organized and firmly bound to the intima. The aneurysmal wall was infiltrated with lymphocytes in many sections. The media was extensively infiltrated with round cells. The lesion was regarded as luetic.

**Discussion.** Aortic abdominal aneurysm is infrequent. Osler<sup>4</sup> found only 16 instances in 18,000 admissions to the medical wards of the Johns Hopkins Hospital. Records of the Hospital of the University of Pennsylvania indicate that on surgical wards these cases are seen even less frequently: in almost 70,000 admissions to the surgical service since 1922, only 5 cases have been definitely diagnosed.

The presenting symptom of patients with abdominal aortic aneurysm is almost always abdominal pain. We have been unable to find a report in which scrotal gangrene was the presenting sign. Although the multiple occlusions of aortic branches might be expected to occur frequently, the complication is rare. A case similar to ours, with occlusion of the inferior mesenteric and hypogastric arteries, could not be found in the comprehen-

sive reviews of Nixon,<sup>3</sup> Bryant,<sup>1</sup> Osler,<sup>4</sup> and Kampmeier.<sup>2</sup> In most instances of abdominal aortic aneurysm, death is due to rupture; in this instance death resulted from gangrene of the large intestine and widespread gangrene of the perineum.

It is frequently difficult to distinguish the pain of tabetic crisis from the pain of an abdominal aneurysm complicated by dissection of the wall or pressure on adjacent viscera or nerves. It was suspected, at the time this patient was admitted, that he was suffering from tabetic crisis, and that the scrotal findings were manifestations of thermal injury. The progress of the disease, especially the development of frank gangrene of the scrotum, indicated, however, that the changes were due to circulatory deficiency. It seems certain that the burn played little or no part in the pathologic process. Occlusion of the right hypogastric artery alone could not have produced bilateral scrotal gangrene. It is thought that gangrene of the left side of the scrotum was caused by multiple small emboli in the branches of the left hypogastric artery, although the lesions were not demonstrated at autopsy.

**Summary.** A rare complication of aortic abdominal aneurysm is reported. A tabetic, admitted to the hospital for scrotal gangrene, developed signs of an abdominal catastrophe and died a few hours after admission. Autopsy showed a saccular aneurysm of the lower abdominal aorta. A thrombus in the inferior mesenteric artery had produced gangrene of the large bowel, while embolic occlusions of the hypogastric arteries were evidently responsible for the scrotal and perineal gangrene.

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## A NEW TYPE OF HEREDITARY HEMOLYTIC JAUNDICE WITHOUT SPHEROCYTOSIS

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(From the Cleveland Clinic)

THE inherited factor in hereditary hemolytic anemia may be either an abnormal shape of the red cell or a qualitative defect in the stroma. In hereditary spherocytosis the fault is an anatomic one, the spherical shape. Congenital ovalocytosis may result in hemolytic anemia. The increased hemolysis seems due to the fact that spherocytes and ovalocytes are removed by the spleen more readily than are normal biconcave disks. The increased hypotonic fragility of the red cells in congenital spherocytosis is directly related to the shape of the cell and degree of spherocytosis. Classic examples of congenital hemolytic anemia in which the stroma is at fault are sickle cell anemia and Mediterranean (Cooley's) anemia. Here there is excessive hemolysis because the cells cannot survive the wear and tear to which erythrocytes are normally subjected.

The term, congenital hemolytic icterus, or anemia, usually refers to hereditary spherocytosis. Ovalocytosis is very rare and produces less anemia. The characteristic clinical picture in congenital spherocytosis is chronic jaundice, usually of mild degree and often noted from birth, anemia and enlarged spleen. The red cells have decreased diameter, increased thickness and decreased fragility in hypotonic salt solutions. The icteric index is increased, and the reticulocyte percentage is increased since the bone marrow tries to compensate for the increased loss of red cells by forming more erythrocytes.

For several years I have observed 2 families which have a characteristic history and the clinical findings of hereditary spherocytic hemolytic icterus but show no spherocytosis. Here there is no explanation for the increased hemolysis. In 1 family the condition has been studied in

3 generations. In the other the disease was found in 2 generations, with a probable history of the same condition in the third generation. This type of hemolytic anemia seems not to have been previously described. The clinical history is identical with that of congenital spherocytosis; each patient has jaundice, anemia and enlarged spleen. All lack the cardinal feature of spherocytosis. All affected members of 1 family show unusual punctate basophilia. Splenectomy in the 1 patient on whom this was tried has not been of benefit. In hereditary spherocytosis the anemia and other symptoms of the disease are always relieved by removal of the spleen, although spherocytosis of the erythrocytes persists. The case histories are as follows:

**Family A.** CASE 1. L. S., aged 25, a native American, entered Cleveland Clinic on Oct. 23, 1939, complaining of pain in the left side of the abdomen. She stated that since birth her eyes had been yellow and at times her skin was yellow. Two years before admission she had begun to have attacks of acute pain in the left upper quadrant. The pain was paroxysmal and severe, and at times a hypodermic injection of morphine was required for relief. With the attacks of pain the jaundice became more intense. One year ago the spleen had been found enlarged.

The patient's mother had died at the age of 26, 1 month after the birth of a child, from a severe anemia which had been diagnosed pernicious anemia. During the pregnancy she had developed a lump (spleen?) in the left side, the removal of which was recommended. Her eyes were often yellow. The patient had 2 children, both boys. She had noted that the older boy was jaundiced at times but had observed nothing abnormal about the other. Both were occasionally irritable and listless. The family history was otherwise entirely negative.

On examination the sclerae were icteric.

The spleen was readily palpable 3 fingers' breadth below the costal margin. The examination showed no other abnormality. The urine on numerous occasions showed no bile, red cells or hemoglobin. Gall bladder Roentgen rays showed no calculi or other abnormality. The Wassermann test was negative.

The blood findings are summarized in Table 1. There was constantly a macrocytic anemia, high reticulocyte count and increased icterus index. The hypotonic fragility was normal. Spherocytes were absent. No hemoglobinemia or spontaneous hemolysis on standing was found. The blood picture was entirely unlike that of congenital spherocytosis.

*Course.* The patient was kept under observation for 2 months. The attacks of severe pain continued, so splenectomy was done on Jan. 12, 1940. The spleen weighed 497 gm. The pathologic diagnosis was chronic hyperplasia, which is not the characteristic finding in the spleen in spherocytic anemia. The patient had some fever throughout the hospital stay of 2 weeks. Frequent blood examinations (Table 1) showed a marked increase in the anemia. The reticulocyte count and icterus index remained elevated. The macrocytosis of the red cells became more marked. This is exactly the reverse of the usual postoperative course in congenital spherocytic anemia after splenectomy. The patient died suddenly 2 days after discharge from the hospital. No autopsy was performed.

**CASE 2.** The older son of Patient 1 was 5 years old when first seen. The mother had noticed that his eyes were sometimes yellow when he was irritable and pepleless. There was no jaundice, and the spleen was not palpable at the initial examination. He did have an anemia with a high (14%) reticulocyte count and a definite hemoglobinemia. He has been seen at intervals for 7 years with little change in the blood findings. These are shown in Table 1. The plasma always contains free hemoglobin, and the red cells hemolyze on standing in a hematocrit tube. The red cells tend to be macrocytic. On successive examinations the spleen has gradually become large and is now 3 fingers' breadth below the costal margin but is not tender. The icterus of the conjunctiva is usually apparent. The urine contains a trace of albumin at times.

Once a slightly positive test for bile was found.

**CASE 3.** D. S., a 3 year old son of Patient 1, had had no illness of any kind, and no jaundice or other abnormality had ever been noted by the mother. The examination was entirely negative. The spleen was not palpable. The blood (Table 1) on the initial examination showed reticulocytosis, a slight increase in icterus index, and free hemoglobin in the plasma. On 2 other occasions the findings were much the same. Two years after the original examination there was a definite icteric tinge to the sclerae, and the spleen was 2 fingers' breadth below the costal margin. Again hemoglobinemia was detected and there was spontaneous hemolysis in the hematocrit tube. The blood findings have remained much the same over a 7 year period. The spleen remains enlarged. No new symptoms have developed. The urine has been negative except for a trace of bile on 1 occasion.

The Donath-Landsteiner test on Patients 2 and 3 was negative. The washed cells of Patient 2, incubated at 37° for 1 hour, showed marked hemolysis with his own, with brother's (Patient 2), and with normal control sera. Control normal cells showed no hemolysis with sera of Patients 2 and 3. These tests show that the defect is in the patient's erythrocytes. The sera of Patient 3 and control treated with N/3 HCl, 0.8% lactic acid, and carbon dioxide shows no hemolysis with patient's and control red cells such as is found in nocturnal paroxysmal hemoglobinuria.

**Family B. CASE 4.** M. S., aged 25, was first seen on Feb. 26, 1945. Her parents were both born in Hungary. The patient was born in this country. She had had the usual childhood diseases but no serious illness. In school she was pale and her eyes were yellow. She was told to see a physician but did not do so. After the birth of her only child, now 4 years old, her physician noted the pallor and jaundice and gave her injections for several years without improvement. At her mother's insistence she was sent to a hospital for study in February 1945. An enlarged spleen was noted for the first time, and hemolytic anemia was diagnosed. Her only symptom has been moderate exhaustion. She has noted a marked difference in the jaundice from time to time. Her stool and urine have never been abnormal.

TABLE 1.—HEMATOLOGIC DATA ON FAMILY A

Name	Date	Red blood cells (mill.)	Hemato-crit (%)	Hemo-globin (%)	Volume index	Color index	Diameter (μ)	Thickness (μ)	Volume thickness (%)	Reticulo-cytes (%)	Icterus index	Hypotonic fragility	Remarks
I. S., Age 25	10/21/39	3.60	80	78	1.11	1.08	8.1	1.95	1.00	14.1	45	44/28	No stippled cells
	1/9/40	3.46	82	81	1.19	1.18	8.0	2.15	1.06	11.8	25	44/28	
	1/12/40		Splenectomy										
	1/12/40	4.01	84	87	1.05	1.04				12.8	25		
	1/15/40	2.53	60	61	1.18	1.20				10.7	22		
	1/17/40	2.52	56	55	1.12	1.10				12.8	15		
	1/19/40	2.63	64	58	1.21	1.09				15.2	12		
	1/22/40	2.59	67	55	1.29	1.06				13.8	8		
	1/24/40	2.89	71	55	1.23	0.95				12.3	8		
	1/26/40	2.85	64	55	1.13	0.96				7.7	10		
W. S., Age 5 (1939)	1/28/40	Died											Def. hemoglobinemia
	10/23/39	3.97	82	81	1.04	1.03	8.0	1.90	0.91	14.0	8	42/28	Def. hemoglobinemia
	1/9/40	4.00	93	91	1.15	1.14	8.0	2.10	1.03	11.7	8	42/28	Free Hb. in plasma
	7/30/40	3.96	84	81	1.06	1.03	8.2	1.80	0.88	13.4	8	42/28	Ring of hemolyzed cells; free Hb. in plasma
D. S., Age 3 (1939)	8/ 5/41	3.95	80	78	1.01	0.99	7.7	1.97	1.01	12.6	10	40/28	No autogglutination
	8/ 8/42	4.07	84	78	1.03	0.96	7.8	1.98	0.99	13.0	15	42/28	No autogglutination
	8/ 3/44	4.14	80	75	0.97	0.90	7.4	2.03	1.10	12.1	15	42/28	No autogglutination
	9/27/46	4.19	82	81	0.91	0.92	7.5	2.00	1.07	15.9	18	44/28	Tr. Hb.; no autogglutination
	10/21/39	3.99	84	78	1.05	0.88	8.2	1.80	0.88	7.3	10	44/28	Def. hemoglobinemia
	1/ 9/40	4.01	80	81	1.00	1.01	8.0	1.85	0.89	7.0	8	44/28	No autogglutination
	7/30/40	3.70	80	71	1.08	0.96	8.0	1.95	0.97	8.7	6	40/28	No autogglutination
	8/ 5/41	4.42	84	78	0.95	0.89	7.3	1.82	0.91	9.8	10	40/28	Free Hb. in plasma; hemolyzed cells
8/ 8/42		3.81	71	63	0.93	0.83	7.6	1.85	0.97	3.3	12	42/28	No autogglutination; free Hb.; little hemolysis
	8/ 3/44	4.39	82	71	0.93	0.81	7.6	1.90	0.97	5.9	6	42/28	Sl. hemolysis after 24 hrs.
9/27/46		4.38	80	81	0.91	0.92	7.5	1.88	0.99	5.3	15	42/28	Hemolysis

TABLE 2.—HEMATOLOGIC DATA ON FAMILY B

Name	Date	Red blood cells (mill.)	Hemato-crit (%)	Hemo-globin (%)	Volume index	Color index	Diameter (μ)	Thickness (μ)	Volume thickness (%)	Reticulo-cytes (%)	Icterus index	Hypotonic fragility	Stippled cells (%)
M. S. (Patient)	2/29/45	3.46	73	61	1.06	0.88	8.0	1.90	0.95	7.0	40	44/34	4.1
	4/25/45	3.47	76	61	1.06	0.88	7.9	2.00	1.10	4.4	35	44/30	
	7/31/45	3.39	73	58	1.07	0.85	8.2	1.85	0.89	5.1	30	44/30	
	3/ 1/46	3.55	76	65	1.07	0.92	7.8	2.00	0.99	6.5	30	44/32	
	7/ 6/46	3.18	71	65	1.11	1.02	7.9			4.9	25	46/32	
	8/29/46	3.02	68	65	1.15	1.08	8.0	2.08	1.03	4.0	40	46/36	
	2/28/45	3.75	76	63	1.01	0.84	7.8	1.90	0.97	4.8	18	48/28	
	4/25/45	4.29	80	65	0.93	0.76	7.9	1.72	0.85	2.3	18	44/30	Marked
	7/31/45	3.92	71	58	0.90	0.74	7.8	1.70	0.87	3.6	15	46/28	Marked
	3/ 6/46	4.98	93	81	0.93	0.81	7.8			1.7	4	42/30	
R. S. (Daughter)	7/ 6/46	3.95	71	62	0.90	0.78	7.8			6.8	18	46/30	
	8/30/46	4.30	80	71	0.93	0.82	8.0	1.63	0.82	0.7	10	44/28	
	2/28/45	3.08	100	84	0.93	0.82	7.6	1.93	1.02	3.5	5	46/34	
	8/29/36	4.95	91	81	0.91	0.82	7.7	1.77	0.90	3.2	4	46/32	
A. V. (Brother)	3/ 5/45	5.20	100	81	0.96	0.78	7.9	1.78	0.89	1.4	5	44/32	
	2/28/45	3.28	71	57	1.08	0.86	7.9	1.98	1.00	1.2	8	42/28	
B. K. (Sister)	3/ 6/46	3.61	71	61	1.16	1.00	7.9			5.4	6	44/32	
	3/ 5/45	3.83	73	65	0.95	0.84	7.9	1.78	0.88	3.8	25	44/34	
C. K. (Sister)	4/25/45	3.90	76	63	0.97	0.81	7.9	1.80	0.88	5.4	13	46/34	
	3/ 6/46	4.16	84	75	1.01	0.90	7.6			3.8	8	44/30	
	7/ 6/46	4.51	89	81	0.99	0.90	7.7			2.9	10	46/32	



On the initial examination there was definite jaundice of sclerae and skin. The spleen was 3 fingers' breadth below the costal margin. The blood pressure was 115/70. There were no other significant findings. All laboratory studies except the blood were negative. The gall bladder functions normally and shows no gall stones. This patient has been seen on 5 occasions since the original examination. She always has jaundice and the spleen is constantly palpable.

The blood (Table 2) shows a constant macrocytic anemia, increased reticulocytes and high icterus index. There is never any evidence of spherocytosis or hemoglobinemia. There is no spontaneous hemolysis. The striking feature of the blood is a constant high percentage of stippled red cells. Hypotonic fragility tests are normal.

The patient's father had been killed in a mine accident many years previously. Her mother was living. She had 1 brother and 2 sisters. These, together with her daughter, were examined (Table 2). The husband is included as a control.

CASE 5. R. S., aged 4, a daughter of Patient 4, had no complaint of any kind and was supposedly well. The relatives had noticed some pallor, but she had had no illness of any kind. On examination the sclerae were icteric and the spleen was 3 fingers' breadth below the costal margin. During the past 18 months she has been seen at intervals. The spleen has remained enlarged. She had developed normally. The blood count has varied. There is a constant anemia and usually an elevated icterus index. The number of stippled erythrocytes and reticulocytes continues high. She has never shown a spherocytosis. Hypotonic fragility tests are normal.

CASE 6. R. S., the mother of Patient 4, was 48 years of age and had had no illness. There was no history of jaundice, enlarged spleen, or gall bladder trouble in the family. She had a yellow tint to the conjunctivae. The spleen was just palpable. She was obese. The examination was otherwise negative. The blood (Table 2) showed no anemia but an increased number of reticulocytes and an abnormal number of cells showing punctate basophilia.

CASE 7. B. K., a sister of Patient 4, had always been well. She was working at a bomber plant when first examined. The examination was negative except for pallor

and a palpable spleen. The condition has remained much the same on 3 succeeding examinations except that the spleen has become larger and the icterus more evident.

The blood showed an anemia on 2 occasions and always an increased reticulocyte count. There was also an increase in cells showing punctate basophilia. There was always a high icterus index. There was no spontaneous hemolysis and a normal fragility test.

CASE 8. J. B., another sister of Patient 4, had never had any illness. She had never noticed anemia or jaundice. The only positive finding on examination was an enlarged spleen and definite jaundice. Her blood (Table 2) showed a macrocytic anemia and reticulocytosis and increased bile content of the plasma. Fragility tests were normal.

CASE 9. A. T., a brother of Patient 4, is included as a control. He had no history of any illness and showed no splenomegaly or jaundice. His blood (Table 2) was normal.

**Discussion.** It is evident that all these patients have a hereditary type of hemolytic anemia. All show an enlarged spleen, anemia, increased reticulocytes and elevated icterus index. The red cells, however, are of normal shape. These tend to be macrocytic. There is no spherocytosis, and hypotonic fragility is normal. A striking feature in 1 family (Family B) is the high percentage of stippled cells.

The defect responsible here for the increased destruction of red cells probably lies in the stroma of the red cells. The presence of free hemoglobin in the plasma indicates that hemolysis is taking place in the circulating blood. The erythrocytes are not simply engulfed and filtered out by the spleen as they are in hereditary spherocytic anemia. The cells may hemolyze spontaneously on standing, and washed cells undergo hemolysis when mixed with normal plasma.

The macrocytosis noted on numerous examinations is characteristic of acquired hemolytic jaundice or any hemolytic jaundice other than that due to spherocytosis. There is no evident explanation for the marked punctate basophilia.

The 1 patient who had a splenectomy was not benefited. After a splenectomy for hereditary spherocytic jaundice, there is a rapid return of the blood to normal, the anemia is relieved, the icterus index returns to normal, and the reticulocytosis disappears. The abnormal shape of the red cells, the spherocytosis, persists, however, throughout the life of the patient. The spherocytes function as well as oxygen carriers as do normal biconcave disks. In the 1 patient in this series who had a splenectomy, the anemia became more marked, and the reticulocytosis and high icterus index persisted until the death of the patient.

**Conclusion.** Eight patients in 2 families are reported, all of whom have hemolytic anemia.

The disease was observed in 3 generations in 1 family and in 2 generations in another, so that it appears to be really hereditary.

The red cells are of normal shape but tend to be macrocytic and to undergo spontaneous hemolysis. Hemoglobinemia has frequently been observed.

Splenectomy in the 1 patient operated upon did not alter the disease.

The condition is probably due to an inherited defect in the stroma of the red cells.

This disease seems to be a new type of hereditary hemolytic jaundice.

## IDIOPATHIC THROMBOCYTOPENIC PURPURA

## A STUDY OF THREE CASES WITH SPECIAL REFERENCE TO CHANGES IN THE MEGAKARYOCYTES

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THE controversy regarding the immediate cause of the thrombocytopenia in idiopathic thrombocytopenic purpura was at first largely speculative, since the early proponents of the 2 major hypotheses did not have the evidence of actual marrow studies on which to base any specific conclusions. In 1915 Frank,<sup>3</sup> in an excellent review of essential thrombocytopenia, suggested the possibility that the disease might be due to a defect in the megakaryocytes leading to depression of platelet production. Kaznelson,<sup>6</sup> on the other hand, in 1916 emphasized the normal status of the few remaining platelets and the presence of giant forms as evidence of the adequate functional capacity of the megakaryocytes in this disease, and on this basis postulated that the thrombocytopenia was dependent on thrombocytolysis. By analogy with the rôle of the spleen in familial hemolytic anemia, he attributed this abnormal function to the spleen. He further supported his views by reporting the first case of thrombocytopenic purpura successfully treated by splenectomy. Dameshek<sup>2</sup> cites Frank's later studies<sup>3a</sup> of the megakaryocytes published in 1925, in which "he noted diminished granularity and greatly diminished platelet production from megakaryocytes, together with the presence of degenerative changes." Willi<sup>19</sup> studied 4 cases of thrombocytopenic purpura by sternal puncture, and although he apparently was not greatly impressed by the degenerative changes in the megakaryocytes, he found very significant the depression of platelet formation which he observed. In his more severe cases evidence of platelet formation was entirely lacking, while in the presence of mild thrombocytopenia it was greatly reduced

and appeared to be largely confined to the promegakaryocytes. Other workers<sup>4,7,10,14,15</sup> have reported abnormalities in the megakaryocytes in this disease, but these have been largely in the nature of degenerative changes. There is fairly general agreement that megakaryocytes are present in significantly increased numbers.

More recently, Limarzi and Schleicher,<sup>8</sup> in a study of the bone marrow in idiopathic thrombocytopenic purpura, have noted the presence of megakaryocytic hyperplasia with an increase in the younger forms (the promegakaryocytes), many of which were seen to be forming non-granular "pseudoplatelets." Many of the megakaryocytes showed a hyaline cytoplasm with absence of azurophilic granules. These changes disappeared following splenectomy.

On the other hand, Wiseman, Doan and Wilson<sup>21</sup> state that sternal marrow studies have consistently revealed "normal numbers of normal appearing megakaryocytes" in cases of idiopathic thrombocytopenic purpura. Others<sup>12,13</sup> have taken essentially the same view.

In many of these studies the platelet forming activity of the megakaryocytes both under normal and abnormal conditions has been largely ignored, and few attempts have been made to break these cells down according to the degree of maturity. Dameshek,<sup>2</sup> however, has recently reported detailed studies of the megakaryocytes in idiopathic thrombocytopenic purpura. The findings were essentially as follows: (1) a relative increase in megakaryocytes with increased percentages of younger forms (megakaryoblasts), and decreased numbers of pro-

megakaryocytes; (2) morphologic changes in the cells, *e. g.*, loss of cytoplasmic granulation and vacuolization; (3) a marked decrease in the percentage of megakaryocytes exhibiting platelet formation; (4) complete reversal of these changes following splenectomy.

Recently 3 cases of idiopathic thrombocytopenic purpura have been available for study in this hospital. Sternal marrow studies, made before and after splenectomy in these cases tended to confirm in the more important respects the observations of Limarzi and Schleicher, and Dameshek. It seemed worthwhile, therefore, in spite of this limited number of cases, to report these findings.

**Methods and Materials.** For this study 11 cases were selected in which sternal marrow aspiration had been performed and in which 1 or more platelet counts were available. These cases covered a wide range of conditions. In addition, peripheral blood and marrow studies were made on 3 cases of idiopathic thrombocytopenic purpura before and after splenectomy. Platelet counts were done in some instances by the Fonio method, in others by the method of Dameshek, and in others both methods were used. All determinations in the 3 cases of idiopathic thrombocytopenic purpura were performed in duplicate.

Sternal puncture was performed with the Turkel needle in the third or fourth interspace, from 0.2 to 0.3 cc. of marrow juice being aspirated. The material obtained was spread immediately on clean slides, dried rapidly in air, and stained with buffered Wright's stain.

The marrow preparations were examined primarily for study of the megakaryocytes, and in each instance at least 100 of these cells were classified. The criteria for differentiation suggested by Dameshek were adhered to as much as possible in classifying megakaryocytes in order that comparable results might be obtained. Experience with the material at hand, however, seemed to indicate that the distribution of megakaryocytes was not sufficiently uniform to allow a reasonably accurate estimate of their relative numbers beyond a statement as to whether these cells appeared to be increased or normal in numbers.

**Results.** The results of the studies in the 11 control cases are given in Table 1. It can be seen that promegakaryocytes and mature megakaryocytes showing definite platelet production constituted the majority of the cells. The total percentage of megakaryocytes showing platelet formation varied from 56 to 80% (average 68.1%). Megakaryoblasts and lymphoid megakaryocytes were rare. Promegakaryocytes varied from 11 to 37% (average 25.2%) and the majority of these exhibited platelet formation. An occasional polykaryocyte or mitotic figure was encountered in these cases. Conditions in which unusual numbers of megakaryocytes are often seen, *i. e.*, 1 of the cases of polycythemia vera and 1 of chronic myelogenous leukemia, showed significant increases in the number of megakaryocytes, and 2 of these, R. S. and S. diC., showed the highest percentages of platelet formation observed, 79 and 80% respectively. This was accompanied by increased peripheral platelet counts. Morphologic variations, such as loss of granulation and vacuolization were rarely observed in this material. In all cases, however, naked megakaryocytic nuclei were a fairly frequent finding. Some of these carried attached masses of platelets.

**Report of Cases.** The cases of idiopathic thrombocytopenic purpura are of some interest, the first because of the presence of rather well-marked lymphadenopathy and the occurrence of myelocytes in the peripheral blood on admission; the second because the age of the patient (54) suggested the possibility of a secondary rather than a primary thrombocytopenia. The clinical and laboratory aspects of both cases, however, supported the diagnosis of the primary disease and the presence of inhibition of normal megakaryocytic activity was regarded as a significant factor in both (Table 2). The third case presented no unusual aspects.

**CASE 1.** R. O'B., a white male of 16 years, entered the hospital May 6, 1946. He had had a tendency to extensive bruising with slight or no trauma since March 1946. A sore throat immediately preceded the onset of the above symptoms. His past history was

TABLE 1.—DIFFERENTIAL COUNTS OF MEGAKARYOCYTES IN CONTROL GROUP

Case	R.B.C. (mill.)	Platelets (thous.)	Promegakaryocytes				Lymphoid		Intermediate		Mature		No. of megakaryocytes	Diagnosis	
			Megakaryoblasts		Megakaryocytes		Megakaryocytes		Megakaryocytes		Megakaryocytes				
			With platelet formation	Without platelet formation	Non-granular platelet formation	With platelet formation	Without platelet formation	With platelet formation	Without platelet formation	With platelet formation	Without platelet formation				
M. S.	9.23	190	1	27	10	0	1	0	4	3	43	11	75	Normal	Non-thrombocytopenic purpura
N. T.	4.52	307	2	26	7	0	0	4	4	4	33	20	63	Normal	Hodgkin's disease
F. S.	4.17	133	0	12	10	0	1	3	0	4	49	22	65	PK1	Lung abscess; empyema
R. S.	3.13	1229	3	27	3	0	0	0	0	0	52	11	79	M1	Chronic myelogenous leukemia
A. C.	6.90	263	2	21	4	2	0	0	0	2	49	20	70	M1	Polycthemia vera?
R. G.	4.03	242	1	13	11	0	0	0	0	4	43	28	56	M1	Multiple myeloma
V. P.	4.20	256	1	20	5	1	0	1	1	0	60	11	80	PK1	Hodgkin's disease
J. H.	4.65	223	1	20	2	1	2	4	1	3	41	25	64	M1	Bleeding peptic ulcer; tertiary lues
S. diC.	9.20	681	1	18	7	0	0	4	2	2	54	12	74	M1	Polycthemia vera
W. O'B.	5.90	236	1	8	5	0	2	3	3	7	43	28	56	Inc.	Polycthemia vera
A. B.	4.30	119	1	9	2	0	0	0	0	5	53	30	62	PK1	Recurrent glioma
Average	..	..	1.2	18.3	6	0.4	0.6	1.7	1.7	3.1	47.1	19.8	68.1		
PK, polykaryocyte. M, mitosis															

P.K. polykaryocyte. M. mitosis

TABLE 2.—ACUTE IDIOPATHIC THROMBOCYTOPENIC PURPURA—DIFFERENTIAL COUNT BY MEGAKARYOCYTES

Date	Case	R.B.C. (mill.)	Platelets (thous.)	Megakaryoblasts	Megakaryocytes										No. of megakaryocytes	Remarks	
					Promegakaryocytes			Lymphoid		Intermediate		Mature					
					With platelet formation	Without platelet formation	N on-granular platelet formation	With platelet formation	Without platelet formation	With platelet formation	Without platelet formation	With platelet formation	Without platelet formation				
1/16/46	1	4.36	37	1	3	18	6	0	0	1	6	7	58	16	Inc.	PK1 M1	Degenerative forms 5%
3/31/46	1	3.72	603	1	17	4	1	0	1	0	6	52	18	70	Inc.	M1	Splenectomy, 5/29/46; marked platelet production
7/8/46	1	4.77	262	0	9	2	0	1	1	8	12	42	25	58	N.	0	4 mos. post-splenectomy; active platelet production
1/14/46	2	5.03	35	1	2	17	9	0	2	2	24	2	41	15	Inc.	0	Degenerative forms 12%
10/10/46	2	3.27	180	1	18	3	0	1	1	4	1	60	11	83	N.	0	Splenectomy, 7/18/46; moderate platelet production
1/15/46	2	5.29	102	1	10	5	4	0	5	8	9	22	36	40	St. inc.	0	3 mos. post-splenectomy; mild recurrence of purpura; moderate platelet production
7/3/46	3	5.07	15	3	7	11	4	2	3	7	11	17	35	33	Inc.	0	Degenerative forms 3%
1/14/46	3	4.30	173	1	11	2	1	2	3	12	6	39	23	64	Inc.	M2	Splenectomy, 9/11/46; moderate platelet production

PK, polykaryocyte, M, mitosis.

P.K. polykaryocyte. M. mitosis.

irrelevant. On admission he exhibited generalized purpuric manifestations, axillary and inguinal adenopathy, and a palpable spleen which extended 4 cm. below the costal margin. The blood studies were within normal limits except for 2% myelocytes and a platelet count of 37,000. No improvement occurred during 3 weeks of medical treatment, and the blood studies did not change significantly except for the disappearance of myelocytes. A lymph node removed for study showed an inflammatory hyperplasia. Sternal aspiration revealed a normal marrow except for changes in the megakaryocytes which are recorded in Table 2. Splenectomy, May 29, 1946, was followed by complete remission of the hemorrhagic manifestation, and an increase in platelets to a peak of 1,500,000 on the 4th postoperative day. The patient made an uneventful recovery and was discharged June 10, 1946. From then until December 1946 platelets have ranged from 55,000 to 262,000 and there has been no recurrence of purpuric manifestations.

CASE 2. E. S., a 54 year old white Jewish housewife, was admitted to the hospital June 11, 1946. Four weeks prior to admission she had had chills, fever and malaise for which she was confined to bed for a few days. One week later bleeding gums and spontaneous bruises were noted. There was nothing of significance in the past medical history. Physical examination revealed no positive findings other than generalized purpuric manifestations. Blood studies were within normal limits except for a platelet count of 17,500. During 4 weeks of medical treatment there was no significant change in her clinical picture or laboratory findings. Splenectomy was performed July 8, 1946, following which she made an uneventful and rapid recovery with complete remission of the disease. The platelets numbered 180,000 48 hours after splenectomy, and had reached a level of 703,000 on the 7th operative day when she was discharged. The patient returned for a check-up Oct. 5, 1946. She had had a recurrence of purpura which was limited to spontaneous ecchymoses of the legs. The platelets at this time numbered 156,000.

Sternal marrow aspirations were performed on June 14, July 10 and October 15. Differential counts of the cells were within normal limits on all 3 occasions except for the changes in the megakaryocytes which are given in Table 2.

CASE 3. S. M., a 32 year old Jewish male, was admitted to the hospital Aug. 28, 1946, with generalized purpuric manifestations which had been present since July 20, 1946. Two years prior to the present illness he had a similar attack which lasted 2 weeks in which purpura was limited to the legs. No studies were made at that time. The past medical history was negative except for frequent headaches for which he habitually took aspirin. Physical examination revealed generalized purpura. The spleen was not palpable. The temperature, pulse and respiration were normal. Blood studies were within normal limits except for a platelet count of 11,000. He was treated medically for 2 weeks with temporary clinical improvement following which purpura recurred. During this time the platelets ranged between 4000 and 15,000. Splenectomy was performed Sept. 11, 1946, and was followed by prompt cessation of purpuric manifestation. The platelets increased to 60,000 in 5 hours, and a peak of 258,000 was reached on the 4th postoperative day. The patient made an uneventful recovery and was discharged Sept. 22, 1946, at which time the platelet count was 61,000. He returned for a check-up Oct. 4, 1946, 23 days after splenectomy. He had had no recurrence of symptoms and platelets numbered 249,000.

Sternal aspirations were done on September 5 and September 14. The differential count of marrow cells was within normal limits except for changes in the megakaryocytes. Studies of these cells are reported in Table 2.

The results of the studies on the megakaryocytes in these 3 cases of idiopathic thrombocytopenic purpura may be seen in Table 2. Preceding splenectomy the megakaryocytes were noticeably increased in numbers in all 3 cases, and platelet production was sharply reduced (Fig. 1). Distribution of the megakaryocytes according to maturity was not significantly different from that of the control group except for a slight increase in megakaryoblasts in Case 3. Changes in the nucleus or cytoplasm regarded as being of a degenerative character occurred in approximately 5% of the megakaryocytes in Case 1, 12% in Case 2, and 3% in Case 3. These changes included an occasional cell

with agranular cytoplasm, but the majority showed sparse, fine granulations with a ragged periphery, vacuolization, or partial extrusion and degeneration of the

karyocytes was seen to be forming non-granular platelets (Fig. 1). In Cases 1 and 3 the megakaryocytes were still increased in number 48 hours following

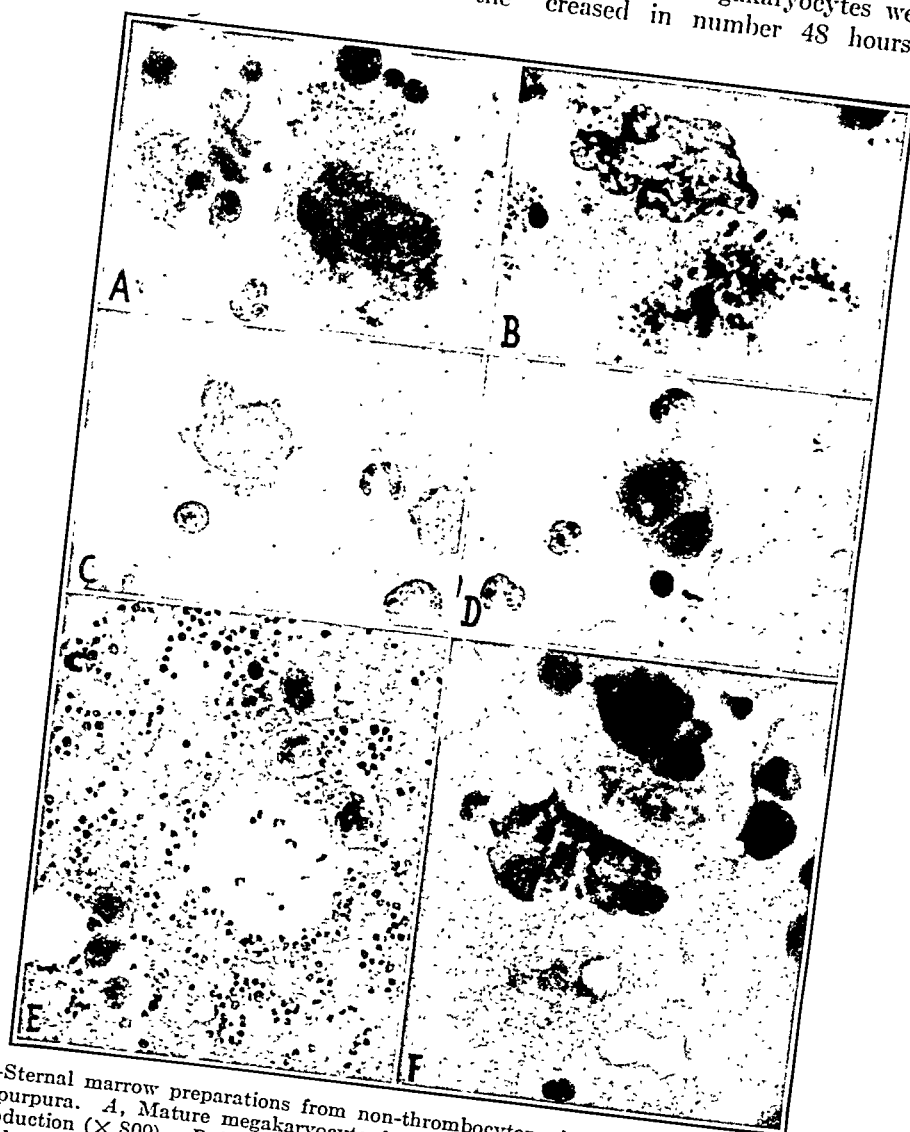


FIG. 1.—Sternal marrow preparations from non-thrombocytopenic cases and idiopathic thrombocytopenic purpura. A, Mature megakaryocyte from normal marrow showing the usual degree of platelet production ( $\times 800$ ). B, Mature megakaryocyte from polycythemia vera showing unusually active platelet formation ( $\times 800$ ). C and D, Thrombocytopenic purpura. Promegakaryocytes producing non-granular platelets ( $\times 800$ ). E, Thrombocytopenic purpura. A typical field exhibiting marked increase in megakaryocytes. None of these cells show platelet formation ( $\times 200$ ). F, Thrombocytopenic purpura. Two mature megakaryocytes with vacuolated cytoplasm ( $\times 800$ ).

nucleus (Fig. 1). Free platelets were seen only rarely in the marrow preparations and most of these showed abnormalities such as agranularity or giant size. In all cases a significant number of promega-

splenectomy while in Case 2 they appeared to be very sparsely scattered. The degenerative changes had largely disappeared and platelet forming activity was markedly increased. The number of

megakaryocytes forming platelets had increased from 15 to 70% in Case 1, from 16 to 83% in Case 2, and from 33 to 58% in Case 3. In Case 1 many of the megakaryocytes bore great masses of platelets representing in many instances more than one-half their cytoplasmic area (Fig. 2) and many large clumps of platelets lay free in the marrow. The platelet forming

above normal levels. It seems probable that a later aspiration in Case 2 might have revealed more striking activity, since the platelets subsequently increased to 703,000. No significant change in the distribution of megakaryocytes was observed following splenectomy in Cases 1 and 2. In Case 3 the percentage of megakaryoblasts decreased to normal levels.



FIG. 2.—Sternal marrow preparations from idiopathic thrombocytopenic purpura 48 hours after splenectomy ( $\times 800$ ). A, Promegakaryocyte actively producing platelets. B and C, Mature megakaryocytes showing massive platelet production.

megakaryocytes showed a marked tendency to occur in clumps. In Cases 2 and 3 the large masses of platelets per cell were lacking, but the percentage of megakaryocytes showing active platelet formation had increased to normal levels. This absence of unusual platelet forming activity may be correlated with the fact that at the time of the sternal aspiration the blood platelets in neither case had risen

**Discussion.** There seems little doubt that when careful and detailed study of the megakaryocytes is made definite abnormalities in these cells may be observed in certain cases of idiopathic thrombocytopenic purpura. Whether the changes are consistently present in all cases remains to be determined. There appears to be some lack of agreement as to the details of these changes, which



may in part be due to individual variations in technique and interpretation. The accumulated observations on the alterations which occur in megakaryocytes have recently been excellently summarized by Dameshek.<sup>2</sup> His own observations have been briefly outlined above.

The results in the 3 cases of idiopathic thrombocytopenic purpura reported herein may be summarized as follows: (1) a definite increase in the number of megakaryocytes; (2) no essential difference in cell distribution when compared to the control cases; (3) a striking decrease in platelet production when compared to the control cases; (4) moderate morphologic changes in the megakaryocytes; (5) active resumption of platelet production 48 hours after splenectomy.

It is evident that these findings differ from those reported by Limarzi and Schleicher,<sup>8</sup> and Dameshek,<sup>2</sup> in that no significant alteration in cell distribution occurred. As was observed by the latter in his cases of acute idiopathic thrombocytopenic purpura, morphologic changes in the megakaryocytes were not striking. Too much emphasis cannot, therefore, be placed upon this feature as a diagnostic criterion in the acute form of the disease. The change which is the most striking, and which appears to be of the greatest significance is the failure of platelet production and the disappearance of this defect following splenectomy.

The inconsistency of the observations of changes in the maturation of the megakaryocytes in idiopathic thrombocytopenic purpura suggests that a considerable degree of individual variation may exist in the megakaryocytic response to the unknown factor which is responsible. The studies of various workers<sup>2,8,10</sup> suggest that some form of maturation arrest is present which is not borne out by the differential counts of megakaryocytes reported above in which the cell distribution did not deviate from the normal and was not appreciably influenced by splenectomy. It seems possible, however, that individual variations such as these might be explained if it is assumed, as was suggested by

Minot,<sup>9</sup> that the point of interference with platelet formation is not primarily with cell development but with the budding off of platelets from the cytoplasm. Such a mechanism might well account for the morphologic changes in these cells, suggesting that rather than using up their substance in the formation of platelets, the megakaryocytes were growing old and degenerating in the marrow without having performed their normal function.

The observation of these distinctive morphologic and functional changes in the megakaryocytes in idiopathic thrombocytopenic purpura seems to be of unusual importance in two respects. It gives promise, first, of being an additional simple and practicable method for differentiating between primary and secondary purpura, and possibly, as suggested by Dameshek,<sup>2</sup> for predicting the value of removal of the spleen in a given case.

It has also a wider significance in its bearing on the controversy regarding the mechanism of hypersplenism. It seems reasonably certain that the inhibition of platelet formation in the marrow could not be entirely the result of thrombocytolytic activity on the part of the spleen. Compensatory hyperplasia of the megakaryocytes with an attendant increase in younger forms might be explained on this basis, but in addition one would expect an increase rather than a decrease in platelet formation. It seems justified, therefore, to regard these findings as evidence of the hypothesis that idiopathic thrombocytopenic purpura is at least in part the result of the selective inhibitory action on the marrow of some substance elaborated by the spleen.

In support of this theory is the accumulating evidence<sup>5,11,17</sup> that injections of extracts of spleens (thrombocytopen) from cases of idiopathic thrombocytopenic purpura are capable of inducing temporary thrombocytopenia in animals. Further investigation of thrombocytopen is necessary before any conclusion regarding its nature can be reached. If this substance represents an internal secretion of the spleen, concentrations of this fraction

of normal spleens should be capable of producing a similar effect in animals. At present injection of crude extracts of normal spleens apparently does not result in thrombocytopenia.

Consideration of these facts leads one to question the soundness of the widely accepted theory that idiopathic thrombocytopenia as an example of selective hypersplenism is due primarily to increased platelet destruction by the spleen.

It is interesting that in all 3 of the cases reported above moderate thrombocytopenia recurred following the postsplenectomy platelet peak, in 1 instance (Case 2) with a mild recurrence of purpura. This type of reaction has been noted frequently by other observers.<sup>1,16,18,20</sup> The final success of splenectomy in these 3 cases must necessarily depend on continued observation, although the experience of others justifies an optimistic prognosis. In Case 3, at least, the mild thrombocytopenia observed 23 days following removal of the spleen apparently was dependent on a depression of the platelet forming activity of the megakaryocytes (Table 2).

This common tendency to temporary or even permanent recurrence of thrombocytopenia following removal of the spleen does not lend itself well to simple explanation. If the view that thrombocytopenia is the result of inhibited megakaryocytic activity is accepted, one might assume the

existence of a temporary instability or irreversible depression of megakaryocytic function which in many cases eventually becomes firmly reestablished at a normal level. On the basis of resumed thrombocytolytic activity a reasonable explanation becomes very difficult. It is to be hoped that continued investigations of the rôle of the spleen and the marrow changes in idiopathic thrombocytopenic purpura will clarify this and other confusing problems related to the disease.

**Conclusions.** 1. In 11 control cases the number of megakaryocytes showing evidence of platelet production varied from 56 to 80% with minimal degenerative changes.

2. Three cases of idiopathic thrombocytopenic purpura showed marked depression of platelet forming activity by the megakaryocytes and a moderate increase in degenerated forms. Forty-eight hours after splenectomy platelet production had returned to normal levels.

3. A sharp increase in platelets occurred in all 3 cases after removal of the spleen reaching a peak within 10 days. This was followed by a temporary fall to thrombocytopenic levels, in 1 case accompanied by a mild recurrence of purpura. In this case moderate thrombocytopenia persisted and was apparently dependent on mild depression of megakaryocytic platelet production.

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## USE OF COLLOIDAL IRON HYDROXIDE FOR THE TREATMENT OF HYPOCHROMIC ANEMIA

### NOTES ON INCIDENCE OF GASTRO-INTESTINAL IRRITATION WITH IRON THERAPY

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THE purpose of this report is to present an iron preparation for oral administration useful in the treatment of hypochromic anemias. Since it is well accepted that iron therapy is essential for hemoglobin production, the problem is one of selection of a preparation which is not only effective, but well tolerated by the patient. It is also widely known that the iron salts now in use may result in unpleasant side reactions which may restrict or hinder adequate treatment. Since this is the result of the large amount of non-absorbed iron remaining in the gastro-intestinal tract, if a preparation is available that offers the same degree of utilization with smaller doses, it would be expected that the incidence of irritation would be less. Colloidal iron in the form of ferric hydroxide because of its chemical and physical properties seemed to us to offer these advantages.

**UTILIZATION OF COLLOIDAL FERRIC HYDROXIDE.** The study was divided into 2 phases. Our first concern was to determine the utilization of the iron when administered orally as colloidal ferric hydroxide.\* In a group of 6 patients, characteristics of whom are presented in Table 1, the rapidity of initial hemoglobin and red blood cell response was determined in order to calculate the daily percentage of iron utilization. These patients were in a chronic disease hospital where they had been observed previously for several months or years, so that their erythropoi-

etic status and response to iron therapy were well known. Hemoglobin determinations were by the use of the Sahli technique and the red blood cell counts were determined by standardized red cell pipettes. Colloidal ferric hydroxide was administered in doses of 75 to 150 mg. 3 times daily, between meals, for a period of 10 days (1 patient was treated for 11 days). The blood tests were repeated at 2 day intervals during the period of observation. The results are summarized in Table 1. The daily utilization of iron varied between 3 and 27.7% and on the average was equivalent to experiences<sup>2,3</sup> with ferrous sulfate in doses of 200 to 400 mg. 3 times daily.

The value of colloidal iron hydroxide for the treatment of hypochromic anemias over prolonged periods of time was studied in a second group of 6 patients. The results are summarized in Table 2. A satisfactory response was obtained in 4 patients. On Patients 5 and 6, an increased amount of the preparation was necessary before a hemoglobin rise occurred. Similar results were obtained previously with the use of ferrous sulfate. As in the case of ferrous sulfate, the maximum rise of hemoglobin and red blood cell counts occurred within the first 5 weeks of therapy.

**GASTRO-INTESTINAL IRRITATION.** To evaluate the incidence of gastro-intestinal irritation resulting from the use of colloidal iron hydroxide as compared with ferrous

\* Each tablet contains 75 mg. ferric hydroxide, equivalent to 39 mg. metallic iron. (This is equivalent to 107 mg. anhydrous ferrous sulfate.) The preparation was supplied by Crookes Laboratories, Inc.

sulfate,\* the preparations were administered to a group of 107 patients who had been hospitalized for a wide variety of medical conditions. None of the patients, however, had any gastro-intestinal disease which might have influenced the results. There was no selection of patient for which preparation was given first. Either

patients were observed with ferrous sulfate. The preparations were administered in doses of either 1 to 2 tablets, 3 times daily and were given 1 hour after meals.

The results are summarized in Table 3. The usual dose of ferrous sulfate produced approximately twice the incidence of gastro-intestinal irritation as compared with

TABLE 1.—UTILIZATION OF COLLOIDAL FERRIC HYDROXIDE FOR THE TREATMENT OF HYPOCHROMIC ANEMIA

No.	Patient	Age	Diagnosis	Control			Daily dose of colloidal ferric hydroxide in terms of iron content (mg.)	Days of treatment	Red cells (mill.)	Hemoglobin		% daily utilization of iron	
				Red cells (mill.)	Hemoglobin					Red cells (mill.)	Hemoglobin		
					Grams	%				Grams	%		
1	L. S.	64	Rheumatoid arthritis; diabetes mellitus	2.9	7.9	54	117	10	3.20	9.7	67	27.7	
2	L. W.	76	Osteoarthritis; essential hypertension	3.4	8.4	58	334	10	3.36	9.1	62	3.0	
3	E. D.	30	Rheumatoid arthritis	4.1	7.3	50	117	10	4.30	8.5	58	17.1	
4	A. R.	88	Generalized arteriosclerosis	4.6	10.8	74	334	10	4.50	12.5	86	8.9	
5	E. B.	70	Pulmonary fibrosis and emphysema	4.2	9.0	62	334	10	4.30	10.2	70	5.9	
6	G. V.	84	Malignancy of colon; arteriosclerosis	3.7	9.5	65	117	11	3.80	11.0	76	23.5	
											Average		14.3

TABLE 2.—EFFECTIVENESS OF COLLOIDAL FERRIC HYDROXIDE FOR THE TREATMENT OF HYPOCHROMIC ANEMIA

No.	Patient	Age	Diagnosis	Control			Daily dose of colloidal ferric hydroxide (mg.)	Days of treatment	Red cells (mill.)	Hemoglobin	
				Red cells (mill.)	Hemoglobin					Red cells (mill.)	Hemoglobin
					Grams	%				Grams	%
1	W. W.	67	Tabes dorsalis	3.76	10.5	72	225	90	4.78	14.0	96.5
2	A. S.	67	Central nervous system syphilis	3.36	8.2	56	225	90	5.03	13.9	96.0
3	J. B.	69	Tabes dorsalis	2.95	8.9	59	225	90	4.38	11.5	79.0
4	R. F.	23	Chronic ulcerative colitis	3.72	10.6	73	450	38	4.44	13.0	89.0
5	M. E. D.	74	Pulmonary fibrosis and em- physema	3.72	9.9	68	225	21	3.31	9.9	68.0
				3.31	9.9	68	450	22	3.37	9.9	68.0
				3.37	9.9	68	675	23	3.60	11.0	76.0
6	B. D.	66	Rheumatoid arthritis	3.58	9.8	67	225	17	3.77	10.3	71.0
				3.77	10.3	71	450	23	3.92	11.3	78.0
				3.68	10.6	73	675	25	3.97	11.5	79.0

drug was administered for a period of 10 to 13 days, unless the onset of gastro-intestinal upsets prevented further therapy. After a suitable rest period, usually 1 week, the other preparation was instituted and followed according to the same regimen. In this way, 91 patients received the colloidal iron hydroxide, while 106

an equivalent dose of colloidal iron hydroxide. As to be expected, doubling the dose resulted in an increased irritation in both instances. Not only was the incidence of irritation less, but also the severity and type of reaction were milder for the colloidal iron hydroxide (Table 3). Constipation was the most frequent untoward

\* The preparation used was ferrous sulfate exsiccated in 0.2 gm. tablets dispensed under the trade name Feosol, manufactured by Smith, Kline & French Laboratories.

reaction noted. Vomiting and abdominal colic were not noted with the colloidal preparation.

**Discussion.** Regardless of the type of anemia, whether primary or secondary, iron therapy is essential for proper restoration of hemoglobin content. For the primary anemias, iron serves as an adjunct. Liver therapy in pernicious anemia results in a marked increase in red blood cells, but unless iron is administered simultaneously, the final result will be a relative

forms are utilized and effective<sup>1,4</sup> for hemoglobin production as long as absorption occurs from the gastro-intestinal tract. In the case of the ferric form, it is undoubtedly altered to the bivalent iron or ferrous state before absorption. Before this could occur, the iron must be made available as soluble salts by the action of the hydrochloric acid of the stomach. Absorption takes place mainly in the upper portions of the small intestine, particularly the duodenum and upper jejunum

TABLE 3.—INCIDENCE OF GASTRO-INTESTINAL SYMPTOMS WITH USE OF COLLOIDAL FERRIC HYDROXIDE AND FERROUS SULFATE

Preparation	Dose in mg. administered 3 times daily	No. subjects	Subjects presenting gastro-intestinal symptoms	
			No.	%
Colloidal ferric hydroxide . . . . .	75	38	3	7.9
	150	53	8	15.1
Total . . . . .		91	11	12.0
Ferrous sulfate . . . . .	200	56	10	17.8
	400	50	15	30.0
Total . . . . .		106	25	23.6

TABLE 4.—TYPE AND INCIDENCE OF GASTRO-INTESTINAL SYMPTOMS FOR COLLOIDAL FERRIC HYDROXIDE AND FERROUS SULFATE

Symptoms	Colloidal ferric hydroxide			Ferrous sulfate		
	Subjects presenting symptoms	Subjects with symptoms (%)	All patients (%)	Subjects* presenting symptoms	Subjects with symptoms (%)	All patients (%)
Constipation . . . . .	7	63.6	7.7	10	38.4	9.5
Diarrhea . . . . .	3	27.2	3.3	7	26.9	6.6
Nausea . . . . .	1	9.2	1.1	4	15.4	3.8
Vomiting . . . . .	0	0	0	1	3.8	0.9
Abdominal colic . . . . .	0	0	0	4	15.4	3.8
Total . . . . .	11		12.0	26		23.6

\* One patient presented 2 complaints.

hemoglobin deficiency. For the hypochromic anemias which make up 90 to 95%<sup>3</sup> of all the anemic states, the "administration of suitable preparations and adequate amounts of iron is the single, most valuable method" for correction of the condition. Emphasis on "suitable preparations and adequate amounts" presupposes that iron medication is administered with full knowledge of its pharmacology.

It is immaterial whether the iron is in the ferrous or ferric state, since both

and is facilitated by an acid medium. Tablets of iron salts that are unduly compressed or coated defeat the purpose of iron medication. There will be insufficient time, not only for adequate action of the gastric hydrochloric acid to result in solubility but also for absorption, since the tablets, before they have become disintegrated, would have traversed those portions of the gut essential for absorption. It is not an uncommon clinical experience to note such intact tablets in the lower portions of the small intestine, colon, or

even rectum upon roentgenologic examination of the abdomen.

Since all iron preparations may result in unpleasant gastro-intestinal symptoms, such as nausea, abdominal colic, constipation, or even diarrhea, they are best prescribed in divided doses, preferably with or immediately after meals. Those preparations which result in good hemoglobin restoration with the smallest prescribed amount are the ones of choice. However, there is no fixed dose for all patients. The requirement varies from patient to patient so that in any particular case, exceedingly large doses may be necessary. Since the iron utilization of any preparation rarely is greater than 15%, the largest amount of the irritable iron salts is unabsorbed and, therefore, available to produce gastro-intestinal irritation.

The principles of iron therapy require, therefore, a preparation which has: (1) an effective hematopoietic response with small amounts, *i. e.*, a high index of utilization; (2) a readily available form for solubility and for action with gastric hydrochloric acid; (3) a low factor of irritability by virtue of its chemical nature and by the small amounts required for good hemoglobin restoration. Iron in the form of colloidal ferric hydroxide satisfies

all of these requirements. Since iron hydroxide, combined with protein, is a normal constituent of foodstuffs, an added advantage is the utilization of a chemical substance existing in nature. Being in the colloidal state, it is more readily soluble in the acid gastric contents than the usual iron salts. Its colloidal nature offers a greater surface area for chemical action with the intestinal contents, thus facilitating alteration to the ferrous state. Utilization is very satisfactory. In regard to gastro-intestinal irritation, results indicate that the incidence of gastro-intestinal symptoms is approximately half that seen with ferrous sulfate. The severity of the gastro-intestinal irritation is also less and its occurrence is more transitory in nature so that the patient could continue the medication without complaint. Many patients unable to tolerate ferrous sulfate have very little difficulty with colloidal iron hydroxide.

**Summary.** Colloidal iron hydroxide is an effective preparation for the treatment of hypochromic anemia. Its daily iron utilization, although equivalent to ferrous sulfate, is achieved with a smaller dose. The incidence and severity of gastro-intestinal complaints noted with its use are less than with ferrous sulfate.

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## STUDIES ON THE ENIGMA OF THE HEMOSTATIC DYSFUNCTION OF HEMOPHILIA\*

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In 1935 the writer with Stanley-Brown and Bancroft,<sup>21</sup> using a newly developed method for the quantitative determination of prothrombin, showed that this clotting factor was normal in hemophilia but was frequently deficient in jaundice. This study which marked the beginning of the application of precise measurement of prothrombin in hemorrhagic diseases also included simple experimental evidence showing that the defect in hemophilia was a deficiency of thromboplastin. This was in accord with the conclusions of earlier investigators whose experiments were essentially qualitative.<sup>17</sup>

If the deficient factor in hemophilia is thromboplastin, it becomes important to know where and how this factor occurs in blood. The earlier investigators, noting that fibrin needles appeared at or near the locus where platelets disintegrated, concluded that these cells furnished the activator of prothrombin, namely thromboplastin. Further support for this view was supplied by the fact that the platelets in hemophilia agglutinate poorly and disintegrate slowly. Gradually, however, more and more evidence has accumulated that the deficient factor in hemophilia resides in the plasma rather than in the platelets. Frank and Hartmann<sup>5</sup> showed that the coagulation time of hemophilic blood was restored to normal by the addition of plasma of a healthy subject. Patek,<sup>11,12</sup> Taylor<sup>12,15</sup> and their associates and Bendien and Creveld<sup>1</sup> isolated from plasma a protein fraction, globulin in nature, which when injected into a hemophilic subject brought the clotting time to normal. Howell<sup>6</sup> in his Carpenter Lec-

ture also took the view that the plasma contains the activator of prothrombin, and advocated using the term plasma thromboplastin. He suggested that the agent was supplied to the plasma by the continuous destruction of platelets. This antihemophilic agent has recently been prepared in a highly concentrated form from normal plasma by the Boston group and it has given effective therapeutic results.<sup>23</sup> Taylor<sup>22</sup> and his associates remain noncommittal as to the exact function of this agent in coagulation by employing the term antihemophilic globulin. Lozner and Taylor,<sup>9</sup> however, on the basis of studies of the influence of various surfaces on the clotting time, concluded that the effect of a foreign surface such as glass is not due to a lysis of platelet but is the result of a physico-chemical alteration of a plasma constituent (globulin substance) with the formation of an active plasma thromboplastin. Earlier Lenggenhager<sup>8</sup> had proposed a similar theory, namely that prothrombokin (comparable to globulin substance) in contact with a foreign surface is converted to thrombokin which combines with calcium and prothrombin to form thrombin. Laggenhager dismissed the platelets entirely as having any rôle in coagulation.

Recently a number of observations have been made which require a reconsideration of the platelets. The writer<sup>16</sup> showed that when oxalated hemophilic plasma was highly centrifuged, it clotted much more slowly on recalcification than the same plasma subjected to a rate of centrifugation which did not remove the platelets (1200 r.p.m.). Jaques *et al.*<sup>7</sup> employ-

\* This work was supported by a grant from the United States Public Health Service.

ing a new water repellant agent, a silicone which effectively delays the clotting of blood, were able to demonstrate clearly that the clotting time in glass of normal plasma was affected by the number of platelets. Feissly<sup>4</sup> in his latest publications has come to the conclusion that the platelets play a major rôle in coagulation and he postulates that they contain both a thermostable and a thermolabile activator of prothrombin.

This state of confusion can be attributed in large part to the lack of quantitative studies and to an overemphasis of the significance of the clotting time. Brinkhous<sup>2</sup> in a notable study was probably the first to use a different quantitative approach. He showed that in hemophilia prothrombin is converted very slowly to thrombin and that this delayed conversion can be corrected by adding thromboplastin. Very recently Chavallier and his associates<sup>3</sup> have also emphasized the high concentration of prothrombin remaining after hemophilic blood has clotted. In the present study, the consumption of prothrombin in the clotting of normal and hemophilic blood has been employed as the key and with this means a series of findings have been made which serve to offer a more concise explanation for the defective coagulation observed in hemophilic blood.

**EXPERIMENTAL.** *A Comparison of the Effect of Progressive Dilution of Thromboplastin on the Prothrombin Time of Normal and Hemophilic Plasma.* Blood was collected in syringes coated with silicone\* and transferred to test tubes also treated with silicone and immersed in an ice bath. By means of high centrifugation, a plasma was obtained which remained fluid in the silicone treated container for several hours. This native plasma obtained from both normal and hemophilic subjects was used to test the effect of decreasing concentrations of thromboplastin. The results are recorded in Table 1.

From these findings one can conclude that hemophilic plasma reacts with throm-

boplastin as readily as does normal plasma; or in other words, the prothrombin of hemophilic blood is converted to thrombin as readily as that of normal blood. The results are contrary to the theory that hemophilic blood contains an antithromboplastic agent. The slightly shorter prothrombin time of normal as compared to hemophilic plasma at high dilutions of thromboplastin can be accounted for by the fact that the former contains a certain amount of plasma thromboplastin which augments the action of the added agent.

*The Thromboplastin Content of Platelets.* Sixty cc. of rabbit blood were mixed immediately after withdrawal with an equal volume of ice cold 10% sodium citrate. The blood was centrifuged for 10 minutes at 800 r.p.m. The plasma obtained was again centrifuged for 10 minutes at the same speed to remove the remaining erythrocytes. The supernatant plasma was then centrifuged at 3000 r.p.m. for 1 hour. The packed platelets were ground with 1 cc. of 0.85% sodium chloride solution and incubated at 50° C. for 20 minutes. The thromboplastin content is indicated by the following experiment:

Oxalated human plasma	0.1 cc.
Platelet extract	0.1 cc.
Calcium chloride 0.02 M	0.1 cc.
Clotting time	80 sec.
Oxalated human plasma	0.1 cc.
Saline solution	0.1 cc.
Calcium chloride 0.02 M	0.1 cc.
Clotting time	100 sec.

These results suggest that the thromboplastin supplied by the platelet extract is very small. It is probable that even this minute amount may have been an impurity rather than an actual product of the platelets themselves.

*The Consumption of Prothrombin in the Coagulation of Normal and Hemophilic Blood.* In order to study the change in the concentration of prothrombin during coagulation, the following test was developed:

Two cc. of blood are transferred to a

\* Mr. J. S. Hurley, Jr., of the General Electric Company kindly supplied the material used in this research. The compound which is methyl-chloro-silane is commercially known as Dri-Film No. 9957.



small pyrex test tube (100 x 13 mm.) and placed in a water bath kept at 37° C. One hour after a solid clot is formed, the tube is centrifuged to separate the serum. To a mixture of 0.1 cc. of thromboplastin and 0.1 cc. of fibrinogen solution, 0.1 cc. of the serum is quickly added by blowing from a pipette, and the coagulation accurately timed. The prothrombin is again determined 3 and 24 hours after coagulation. The test for the 1 hour serum is not always entirely accurate since a variable quantity of free thrombin may be present which in 2 or 3 hours is converted to inactive metathrombin.

From the results in Table 2, it can be concluded that the amount of prothrombin used up in the clotting of hemophilic blood is so small that it cannot be satisfactorily measured. It should be noted that the concentration of prothrombin even after 24 hours is essentially unchanged. In marked contrast, approximately 80 to 85 % of the prothrombin is converted to thrombin within 1 hour after the coagulation of normal blood. It is very likely that almost all of this conversion occurs during the period of active coagulation, *i. e.*, within the first 10 minutes, but since much free thrombin is present, a satisfactory

TABLE 1.—THE INFLUENCE OF THE CONCENTRATION OF THROMBOPLASTIN ON THE PROTHROMBIN TIME OF NATIVE HEMOPHILIC AND OF NORMAL PLASMA

Concentration of thromboplastin (%)	Prothrombin time*		Concentration of thromboplastin (%)	Prothrombin time*	
	Hemophilic plasma (sec.)	Normal plasma (sec.)		Hemophilic plasma (sec.)	Normal plasma (sec.)
100 . . . .	12	12	5 . . . .	24	25
75 . . . .	13	13	2 . . . .	35	34
50 . . . .	14	14	1 . . . .	52	47
20 . . . .	17	17	0.5 . . . .	69	63
10 . . . .	19	18	0 . . . .	3600	120

\* One-tenth cc. of native plasma was mixed with 0.1 cc. of saline solution and 0.1 cc. of thromboplastin quickly added.

Dehydrated rabbit brain (200 mg.) was mixed with 5 cc. of saline solution and incubated at 50° C. for 20 minutes. For preparing the dilutions, the supernatant liquid was used.

The thromboplastin is prepared from rabbit brain dehydrated with acetone according to the author's method. Unless the preparation yields a prothrombin time of 12 seconds for fresh human oxalated plasma, it is not suitable for the test.

The fibrinogen solution is prepared from citrated rabbit\* plasma, which is first treated with aluminum hydroxide to remove prothrombin (component B). One volume of the treated plasma is mixed with 1.2 volumes of saturated sodium chloride solution in a conical centrifuge tube. The fibrinogen which is salted out is centrifuged off and packed into a small volume. The tube is rinsed with distilled water and the fibrinogen dissolved in 0.3 % sodium chloride solution and brought to the same volume as that of the original plasma.

determination is not possible. Little prothrombin is consumed after the 1st hour. It is rather surprising that a considerable quantity of prothrombin, often 10 % or more, remains unchanged in the clotting of normal blood. There seems to be considerable variation in the prothrombin consumption of normal subjects but the cause is entirely unknown.

*The Effect of Added Normal Plasma and of Thromboplastin on the Prothrombin Conversion of Hemophilic Blood.* In order to determine whether normal plasma or thromboplastin in the form of a rabbit brain extract when added to hemophilic blood would increase the consumption of prothrombin, the experiments summarized in Tables 3 and 4 were undertaken.

It is obvious that both plasma and thromboplastin increase the amount of

\* \* More recent observations suggest that human fibrinogen may yield somewhat more reliable results.

prothrombin used up in coagulation and it is logical to assume that both contain the specific activator of prothrombin. Since thromboplastin injected intravenously causes intravascular clotting, while plasma by the same route does not, it seems certain that the agent in plasma is different for the substance found in tissue extracts. In the latter, the activator is free and immediately reactive, whereas in plasma it is inactive as will be shown by subsequent data.

sure the coagulation time is also reduced to normal, but it is much more probable that the greater conversion of prothrombin is responsible for the normal hemostatic response that permitted for instance a major operation without any abnormal bleeding. Similar findings were made in a patient given plasma for a tooth extraction. Apparently when the thromboplastic agent, or perhaps more correctly, the thromboplastin precursor is supplied by a transfusion, it is only gradually used

TABLE 2.—COMPARISON OF THE PROTHROMBIN CONSUMPTION IN THE COAGULATION OF NORMAL AND OF HEMOPHILIC BLOOD

		Lee White coagulation time (min.)	Prothrombin time of serum		
			1 hr.* (sec.)	3 hrs.* (sec.)	24 hrs.* (sec.)
Normal	I . . . . .	7	27 (19)	33 (13)	40 (9)
	II . . . . .	8	30 (15)	34 (13)	34 (13)
	III . . . . .	9	32 (14)	32 (14)	37 (11)
Hemophilic	I . . . . .	25	10½ (100)	11 (100)	10½ (100)
	II . . . . .	65	10 (100)	10 (100)	11½ (100)
	III . . . . .	140	11 (100)	10½ (100)	11 (100)

\* After a solid clot formed.

The figures in parenthesis are the approximate prothrombin concentrations in % of normal.

TABLE 3.—CHANGES IN THE PROTHROMBIN CONSUMPTION IN THE COAGULATION OF HEMOPHILIC BLOOD AFTER THE IN VITRO ADDITION OF NORMAL PLASMA AND OF THROMBOPLASTIN

Hemophilic blood	cc. . . . .	2	2	2	2	2	2
Normal plasma	cc. . . . .	..	0 02	0 05	0 1	..	..
Thromboplastin	cc. . . . .	..	..	..	..	0 04	0 2
Coagulation time	sec. . . . .	1680	300	270	270	30	17
Prothrombin time	1 hr. sec. . . . .	10 (100)	12½ (80)	13½ (60)	15 (50)	19 (30)	34 (13)
"	" 3 hrs. sec. . . . .	11 (100)	12½ (80)	14 (55)	17 (40)	19 (30)	35 (13)
"	" 24 hrs. sec. . . . .	10 (100)	12½ (80)	14 (55)	18 (35)	19 (30)	33 (13)

The figures in parenthesis are the approximate prothrombin concentrations in % of normal.

TABLE 4.—THE EFFECT OF INTRAVENOUSLY ADMINISTERED LYOPHILE HUMAN PLASMA ON THE PROTHROMBIN UTILIZATION IN THE COAGULATION OF HEMOPHILIC BLOOD

		Lee White coagulation time (min.)	Prothrombin time of serum		
			1 hr. (sec.)	3 hrs. (sec.)	24 hrs. (sec.)
Before transfusion		60	9½	10	11
After injecting 250 cc. of plasma*		9	..	19	24
2 hours after the injection of 250 cc. additional		8	18½	..	27
After 24 hrs.		9½	17	..	23
After 72 hrs.		25	14	..	15½

\* After 250 cc. of plasma had been injected, a tenotomy operation for lengthening the heel cord was performed by Dr. Walter Blount. No abnormal bleeding was encountered. The wound was dressed and the leg put in a plaster cast. Healing was normal. Bleeding was encountered when the stitches were removed 2 weeks after the operation, but it was controllable by local measures.

Of great significance is the fact that a plasma transfusion causes a sustained improvement in coagulation as measured by the prothrombin consumption test. To be

up and therefore this treatment gives the patient a period of safety which is not unlike that of injecting fibrinogen in the form of plasma in afibrinogenemia, or prothrom-

bin in congenital hypoprothrombinemia. In all 3 conditions a quantitative lack of a basic factor needed in coagulation exists which can be temporarily corrected.

*The Influence of Platelets on the Conversion of Prothrombin to Thrombin.* By coating the syringe and needle with silicone, blood can be withdrawn without causing more than a slight or negligible disintegration of platelets. On transferring the blood to a test tube (likewise

Obviously the removal of platelets markedly reduces the conversion of prothrombin. Thus, only a small amount of prothrombin was consumed in 3 hours as seen in Table 4. Even after 24 hours the loss of prothrombin is relatively little. In marked contrast the plasma in which the platelets were retained, clotted faster and the prothrombin was much more reduced even during the 1st hour. It is highly probable that with a highly refined

TABLE 5.—THE INFLUENCE OF PLATELETS ON THE CONSUMPTION OF PROTHROMBIN DURING THE COAGULATION OF NORMAL HUMAN PLASMA

	Coagulation time§ (min.)	Prothrombin time of serum		
		1 hr. (sec.)	3 hrs. (sec.)	24 hrs. (sec.)
Plasma I:*				
Highly centrifuged†	10	10 (100)	11 (100)	13 (70)
Slowly centrifuged‡	6	25 (20)	25 (20)	24 (20)
Plasma II:*				
Highly centrifuged†	24	10 (100)	10½ (100)	11 (100)
Slowly centrifuged‡	7	24 (20)	25 (20)	27 (19)

\* Both bloods had a coagulation time of 7 minutes by the Lee White method.

† 4000 r.p.m.

‡ 1200 r.p.m.

§ The coagulation time of plasma was determined by using complete opacity as the end point. The figures in parenthesis are the approximate concentrations of prothrombin in per cent of normal.

TABLE 6.—THE EFFECT OF PLATELETS ON THE CONVERSION OF PROTHROMBIN TO THROMBIN IN MIXTURES OF HEMOPHILIC AND NORMAL PLASMAS

No.	Mixtures	Lee White coagulation time (min.)	Prothrombin time of serum		
			1 hr. (sec.)	3 hrs. (sec.)	24 hrs. (sec.)
1.	Hemophilic plasma (high centrifugation)	0.5 cc.			
	Normal plasma (high centrifugation)	0.5 cc.	10	9	11
2.	Hemophilic plasma (slow centrifugation)	0.5 cc.			
	Normal plasma (high centrifugation)	0.5 cc.	4½	11	14
3.	Hemophilic plasma (slow centrifugation)	0.5 cc.			
	Normal plasma (slow centrifugation)	0.5 cc.	4	14	16½
4.	Hemophilic plasma (high centrifugation)	0.5 cc.			
	Normal plasma (slow centrifugation)	0.5 cc.	4	12	15
5.	Normal plasma (high centrifugation)	1.0 cc.	10	10½	11
6.	Normal plasma (slow centrifugation)	1.0 cc.	6	26	26

For high centrifugation the angle centrifuge was employed at a speed of 4000 r.p.m.; for slow speed a standard centrifuge at 1200 r.p.m. was used.

coated with silicone) and centrifuging it at a relatively high speed (7 minutes in an angle centrifuge at 3500 r.p.m.) a plasma is obtainable which contains very few platelets. Such a plasma definitely clots slower than one obtained by slow centrifugation and exhibits no clot retraction. A comparison of the prothrombin consumption during coagulation of plasma with and without platelets is given in Table 5.

technique which would enable one to remove all the platelets before any disintegration occurred, an incoagulable plasma could be obtained; but even with the present relatively platelet-free plasma, the defective coagulation is striking. Nevertheless, this platelet-free plasma, when added to hemophilic blood, supplies the missing coagulant which is presumably thromboplastin. This suggests that the thromboplastin factor is not free in plasma,

but appears to be activated by the disintegration of platelets.

To test this hypothesis further, the changes in prothrombin were studied using various mixtures of hemophilic and normal plasmas which were allowed to clot. A typical finding is recorded in Table 6. A study of these results shows clearly that platelets are necessary for the conversion of prothrombin to thrombin. The addition of normal platelet-free plasma to hemophilic plasma likewise deprived of platelets (Mixture 1) did not improve coagulation as measured by prothrombin conversion. The presence of platelets whether from hemophilic plasma (Mixture 2) or from the normal plasma (Mixture 4) brought about better coagulation and a greater consumption of prothrombin. This can be considered to be fairly clear-cut evidence that hemophilic platelets are equally as active as those of normal blood. Since hemophilic blood lacks thromboplastin, the activity of hemophilic platelets cannot be due to their thromboplastin content, but due to an action that they exert on some agent present in normal blood which can be postulated to be the precursor of thromboplastin.

*Observations on the Coagulation Time of Hemophilic Blood.* It has been observed by various investigators that the actual process of coagulation of hemophilic blood, i. e., from the incipient appearance of fibrin to the complete conversion of fibrinogen covers a long period of time, in contrast to the exceedingly rapid completion of coagulation of normal blood once it is begun. This can be effectively demonstrated by placing a glass rod coated with collodion, which has an affinity for fibrin, in a test tube containing 1 cc. of hemophilic blood. By carefully withdrawing the rod at fixed intervals of time, the beginning of coagulation can be detected by a minute thread of fibrin adhering to the rod. As an example, a hemophilic blood thus tested showed a fibrin thread in 10 minutes yet required 2 hours and 20 minutes before a solid clot formed. But even a solid clot is not a reliable measure

of complete coagulation. Thus, in a hemophilic blood which gave a solid clot in 45 minutes, unchanged fibrinogen could be demonstrated in the serum for over 1 hour more.

The striking effect of a minute quantity of thromboplastin on the coagulation time is illustrated by the following experiment. To 1 cc. of hemophilic blood, which had a coagulation time of 2 hours and 15 minutes, was added 0.1 cc. of thromboplastin (an emulsion made by mixing 200 mg. dehydrated rabbit brain with 5 cc. saline solution) diluted 1 to 1000 with saline. The coagulation time was reduced to 5 minutes. Thus, the addition of 0.1 cc. of highly diluted thromboplastin which contained only 2.5 gammas of solid material in solution, of which the greater part was inert, reduced the coagulation time to normal. No detectable conversion of prothrombin, however, occurred. This finding can readily be explained. The addition of even a minute amount of thromboplastin produces an equivalent quantity of thrombin, which being an enzyme, converts fibrinogen slowly but continuously to fibrin, so that in spite of its minuteness in amount, it coagulates enough fibrinogen in a few minutes to form a solid mass.

**Discussion.** In the experiments presented in this study, it should be noted that nearly all observations were made on blood or plasma that had been little altered by external factors. Every attempt was made to preserve the delicate physico-chemical balance of the blood. By exceedingly simple means a number of significant observations on the behavior of hemophilic blood were made.

Fundamentally, the defective hemostasis of hemophilia is due to a lack of available thromboplastin in the blood. The prothrombin is normal both quantitatively and qualitatively. As shown in Table 1, the activity of hemophilic prothrombin is equal to that of normal blood. Due to the lack of thromboplastin in hemophilic blood, very little prothrombin becomes converted in thrombin. It is not as Brink-

hous<sup>2</sup> concluded, a slow conversion of prothrombin to thrombin, but a quantitative lack of conversion.

There is good evidence that the reaction, prothrombin + thromboplastin + calcium = thrombin, is stoichiometric (Mertz, Seegers and Smith<sup>10</sup>). From the present data one can conclude that normal plasma contains enough available thromboplastin to convert 80 to 90% of the prothrombin to thrombin. By giving a hemophilic patient a plasma transfusion, sufficient thromboplastin can be supplied to maintain effective hemostasis for 24 to 48 hours, as seen in Table 4. The loss of adequate hemostasis runs parallel with the lack of prothrombin conversion as measured by the new test described. Apparently a certain amount of thrombin must become available promptly if satisfactory stanching is to be achieved. Fortunately normal blood contains an excess of both prothrombin and thromboplastin. A decrease of either agent leads to the same end result, namely, a deficiency of thrombin. In the case of prothrombin, a decrease to 20 to 30% of normal brings the blood into the potential hemorrhagic zone. Although the present studies can be considered to be fairly quantitative, more data will be necessary before the danger level of thromboplastin can be defined. It should be emphasized that the determination of the consumption of prothrombin offers the first promising means for assaying the thromboplastic activity of blood.

The coagulation time, as becomes obvious from the above discussion, is of limited value as a measure of hemostatic effectiveness. It is well known that a normal coagulation time is not uncommonly obtained even when the prothrombin is reduced below the hemorrhagic level. In the case of hemophilia the coagulation time is a somewhat better guide, but unfortunately even in this condition a temporary reduction of the clotting time to normal (carefully determined by the Lee White procedure) does not necessarily assure good hemostasis. As pointed out before, an extremely small quantity of

thromboplastin will cause the formation of sufficient thrombin to convert a large amount of fibrinogen to fibrin in a test tube. The same amount of thrombin *in vivo* would be quickly dissipated by dilution and inactivation. Assuredly, much greater caution must be exercised in interpreting the clinical significance of hyper- and hypocoagulability than has been done heretofore. Surprisingly, the coagulation time when carefully determined may remain remarkably constant in a hemophilic for a long period of time. The writer has studied continuously 3 hemophilic subjects from 3 to 17 months. In 1 the coagulation time has varied with few exceptions from 2 hours to 2 hours and 20 minutes, in the second from 25 to 35 minutes, and in the third from 45 to 65 minutes. Although these differences appear striking, all 3 suffered about the same number of bleeding episodes in a comparable period of time. In none is sufficient prothrombin consumed to allow an estimation of the amount.

The results obtained in the present investigation clearly show that the platelets are essential for coagulation since they appear to be required for the activation of the thromboplastin which is present in the plasma in an inactive form. Lenggenhager<sup>8</sup> who has likewise postulated the presence of an inactive precursor in plasma has named it prothrombokinin. Since the name of the activator of prothrombin now generally accepted is thromboplastin, the term for the precursor should preferably be either prothromboplastin or thromboplastinogen, and of these the latter term is more desirable because it is more euphonious. From the results recorded in Tables 5 and 6, one can conclude that the platelets are responsible for the activation of the thromboplastinogen. It appears that platelets on disintegration liberate an enzyme which acts specifically on this precursor of thromboplastin. Hemophilic platelets would thus be normal in function, but have no thromboplastinogen to convert. As soon as this material is supplied by a transfusion of normal plasma, the

hemophilic platelets react, and fairly normal coagulation is established.

The agglutination and disintegration of platelets appear to be contingent upon the formation of thrombin. Pinniger and Prunty<sup>13</sup> have observed that progressive alterations of platelets occurred in afibrinogenemic blood soon after it came in contact with glass. Pinniger<sup>14</sup> has further found that thrombin is formed in such blood. Apparently therefore the agglutination of platelets is independent of fibrin. In hemophilic blood in which the production of thrombin is very minute, the platelets remain unaltered. This suggests that the production of thrombin is related to platelet disintegration and it may well be that the following chain reaction is set up: formation of thrombin brings about the disintegration of platelets which in turn makes more thromboplastin available to form more thrombin. The coagulation of normal blood characterized by a latent period followed by a rapid conversion of fibrinogen to fibrin strongly suggests such a chain reaction.

From the foregoing discussion one can postulate that 3 essential steps occur in the coagulation of blood:

1. Thromboplastinogen + platelet enzyme  $\rightarrow$  thromboplastin.
2. Prothrombin + thromboplastin + calcium  $\rightarrow$  thrombin.
3. Fibrinogen + thrombin  $\rightarrow$  fibrin.

Two of the reactions are presumably enzymatic while one is stoichiometric. The process undoubtedly is more complex than indicated by these skeleton equations.

As already intimated, the action of platelets requires further study to determine their exact mode of action. It is probably that clotting in response to injury is often initiated by the entrance of tissue juice into the blood, but the effective completion entails the disintegration of platelets and the conversion of the thromboplastin precursor to the active form. The activation of prothrombin is complicated by the fact that apparently this factor consists of 2 components.<sup>19</sup> Even the rôle of calcium is not understood.<sup>20</sup> In hemophilia the defect is in the second step, namely insufficient available thromboplastin in the blood to form an adequate amount of thrombin. The enigma why this deficiency occurs remains unsolved.

**Summary.** Evidence has been presented to show that the hemostatic dysfunction in hemophilia is due to a lack of available thromboplastin in the blood. This causes an insufficient production of thrombin as shown by the fact that very little prothrombin is consumed in the coagulation of hemophilic blood.

Results have been obtained that indicate that the thromboplastin of normal blood is present in the plasma in an inactive form, designated as thromboplastinogen, which is changed to active thromboplastin by the action of substances from the platelets.

The limitations of the coagulation time as an indicator of hemostatic efficiency are discussed.

The coagulation is described as consisting of 3 fundamental steps: (1) the activation of thromboplastinogen, (2) the formation of thrombin and (3) the conversion of fibrinogen to fibrin.

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# THE RELATIONSHIP OF GLUTAMIC AND ASPARTIC ACIDS TO THE PRODUCTION OF NAUSEA AND VOMITING IN MAN

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In previous work<sup>6</sup> it was found that certain amino acid preparations obtained by the hydrolysis of casein, when administered intravenously to human subjects, produced a depression in voluntary food intake, whereas a mixture of the 10 "essential" amino acids did not cause a reduction in the appetite. Also, during the course of that study, it was observed that if the casein hydrolysates here administered at relatively rapid rates, nausea and vomiting were likely to occur. The observations which form the basis for this report were made in an attempt to determine the contributing factors responsible for these undesirable effects.

It has been reported<sup>2,3,7</sup> that the addition of either glutamic or aspartic acid to known amino acid mixtures, when given intravenously to dogs, greatly reduced the tolerance of these mixtures. Because the mixture of amino acids developed by Madden and Clay<sup>9</sup> and designated by them as "VUJ"\* failed to produce anorexia, nausea and vomiting the likelihood of other amino acids being responsible was evident. It was decided to determine whether the dicarboxylic amino acids would produce nausea or vomiting when administered intravenously to human subjects.

A test dose of 0.82 gm. of l-glutamic acid (Merck) dissolved in 500 cc. of an 8% solution of "VUJ" mixture was administered to the first 3 subjects in these investigations. In subsequent studies with other subjects, the amount of glu-

tamic acid was increased to 8.2 gm. dissolved in either 500 cc. of an 8% solution of "VUJ" mixture or in water. In all instances the glutamic acid was partially neutralized with sodium bicarbonate to bring the pH of the mixture approximately to that of the original "VUJ" mixture. The material was steam sterilized before administration.

From calculations based on the nitrogen content of the "VUJ" it was concluded that 1500 cc. of "VUJ" solution (3 bottles) was equivalent to about 100 gm. of protein. Since casein contains approximately 24.6 gm. % glutamic acid,<sup>1</sup> the amino acids derived from 100 gm. of casein would contain about 24.6 gm. of glutamic acid. The dose of 8.2 gm. of glutamic acid per 500 cc. of 8% of "VUJ" mixture is the amount of glutamic acid which would be present in the amino acid mixture "VUJ," if it were derived from casein.

dl-Aspartic acid (Merck) was administered to all the subjects in these experiments at a concentration of 2.1 gm. per 500 cc. of 8% "VUJ" mixture. This amount was likewise based on the estimate that casein contains 6.3% aspartic acid.<sup>1</sup> All samples were steam sterilized before administration. No attempt was made to neutralize the small amount of aspartic acid which was added to the "VUJ" mixture.

The subjects used in this study were ward patients and were chosen on the basis of their willingness to cooperate;

\* The amino acid mixture "VUJ" contains the 10 essential amino acids plus glycine and 50% of its amino acids are in racemic form. This mixture was supplied through the courtesy of Merck and Company, Inc., Rahway, N. J.



only those individuals with good veins were selected. During the course of this work some subjects whose voluntary food consumption was being estimated received 3 infusions of the supplemented "VUJ" solution per day for 3 days, while the others received only a single infusion. As a control, unsupplemented "VUJ" solution was administered intravenously to 9 patients. Most of the subjects were given infusions at rates approximating 16 cc. per minute. Due to technical difficulties in administration, a few received the infusions at a slower rate.

tolerated 9 doses of "VUJ" fortified with glutamic acid without experiencing either nausea or vomiting. With the administration of this preparation occlusion of the veins was a common occurrence. This was probably due to the hypertonicity of the material since the solution used contained, in addition to the 8% "VUJ" solution, 8.2 gm. of glutamic acid and approximately 2 gm. of sodium bicarbonate. Five subjects received 8.2 gm. of partially neutralized glutamic acid dissolved in water. In this group, 2 subjects vomited and 2 became dizzy. Of the

TABLE 1.—THE EFFECT OF INTRAVENOUSLY ADMINISTERED GLUTAMIC ACID ON THE PRODUCTION OF NAUSEA OR VOMITING

(The glutamic acid was dissolved in either 500 cc. or "VUJ" or water)

Subject No.	Initials	Sex	Glutamic acid		Rate (cc./min.)	Reaction
			In "VUJ" (gm.)	In water (gm.)		
1	G. F.*	M	0.82	..	16	Vomited
2	F. C.*	M	0.82	..	17	Nausea
3	F. S.*	M	0.82	..	16	0
			8.20	..	17	0
4	L. B.*	M	8.20	..	As fast as 45	0
5	W. S.*	M	8.20	..	"	0
6	D. O.*	M	8.20	..	"	0
7	M. B.	F	8.20	..	16	Vomited
8	F. D.	M	8.20	..	16	"
9	F. G.	M	8.20	..	16	0
				8.2	16	Dizzy
10	E. E.	M	8.20	..	16	Vomited
11	A. N.	M	8.20	..	16	"
				8.2	16	"
12	A. S.	M	8.20	..	17	0
				8.2	17	Vomited
13	G. S.	M	..	8.2	16	Dizzy
14	K. S.	M	..	8.2	8	0
15	G. C.	M	8.20	..	20	Vomited
16	W. S.	M	8.20	..	12.5	Nausea
17	H. J.	M	8.20	..	12.5	"

\* These subjects received 3 doses of the glutamic acid containing "VUJ" for 3 consecutive days.

**Results.** Glutamic acid was administered intravenously to 17 patients. The results of this investigation are summarized in Table 1. Of the 3 patients who received 0.82 gm. of glutamic acid dissolved in "VUJ," 1 vomited and another became nauseated. Thirteen subjects were given 8.2 gm. of glutamic acid dissolved in "VUJ" and of these 5 vomited. One subject received both concentrations of glutamic acid and experienced no ill-effects with either. It is of interest that certain patients, such as Nos. 3, 4, 5 and 6 each

entire group of 17 subjects who received glutamic acid dissolved in either "VUJ" or water, 8 vomited and 3 became nauseated.

The results of the administration of dl-aspartic acid added to 8% "VUJ" solution, are summarized in Table 2. In this series 13 subjects received the test dose; of these, 1 became flushed and 4 complained of nausea.

The 8% "VUJ" solution alone was administered intravenously to 9 patients. These subjects constituted an excellent

control group and together they received a total of 41 infusions of 500 cc. each. The rate of administration varied from 17 to 45 cc. per minute. In no instance did vomiting occur and none of the patients in this group complained of nausea.

tures now available for clinical use. The amounts of glutamic and aspartic acids administered were derived by calculation from the data of Block and Bolling<sup>1</sup> on the amino acid content of casein. The quantity of these dicarboxylic acids given was

TABLE 2.—THE EFFECT OF INTRAVENOUSLY ADMINISTERED ASPARTIC ACID ON THE PRODUCTION OF NAUSEA

(The aspartic acid, 2.16 gm., was dissolved in 500 cc. of "VUJ" mixture)

Subject No.	Initials	Sex	Rate (cc./min.)	Reactions
4	L. B.*	M	8	0
5	W. O.*	M	13	0
6	D. O.*	M	15	0
18	I. P.	M	33	0
19	M. S.	M	33	Flushed
20	G. G.	M	20	Nausea
21	O. U.	M	9	0
22	C. C.	M	7	0
23	T. W.	M	17	Nausea
24	B. H.	M	19	0
25	W. S.	M	8	Nausea
26	H. C.	M	25	0
27	A. G.	M	23	Nausea

\* These subjects received 3 infusions of "VUJ" containing aspartic acid per day for 3 consecutive days.

**Discussion.** The amino acid mixture "VUJ", which does not contain any so-called "non-essential" amino acids other than glycine, can be administered at a rapid rate without producing either nausea or vomiting. This mixture presented an ideal vehicle for testing in humans the hypothesis proposed by Madden and his co-workers<sup>2,3</sup> that glutamic and aspartic acids are the factors in protein hydrolysates which reduce the tolerance to these preparations when administered intravenously to dogs. From the observations which form the basis of the present report, it appears that glutamic acid when administered intravenously has a definite tendency to produce nausea and vomiting in man. On the other hand, undesirable reactions occur less frequently when aspartic acid is administered intravenously. It should be pointed out that a smaller amount of aspartic acid than glutamic acid was given. The reason for selecting the doses used in these studies was to obtain the concentrations of these amino acids comparable to those present in the preparations of amino acid mix-

considered to be that which would appear in a casein hydrolysate equivalent to 500 cc. of 8% "VUJ" mixture. It appears that glutamic acid must be administered intravenously to have an emetic effect. Price, Waelsch and Putnam<sup>5</sup> have given 16 to 20 gm. of this acid orally to epileptic patients and only 1 of their 8 cases complained of gastric symptoms.

The data presented here on human subjects are consistent in a qualitative sense with those of Madden and associates<sup>2,3</sup> and also of Unna and Howe,<sup>7</sup> who showed that both glutamic and aspartic acids produced vomiting in dogs.

In 6 patients who received the "VUJ" solution to which glutamic acid was added the influence of this mixture upon the amount of food voluntarily consumed was observed. The method used in determining the influence of amino acid preparations on the voluntary food intake was the same as that previously described.<sup>6</sup> The quantity of glutamic acid administered daily to 4 of these subjects was 24.6 gm. dissolved in 1500 cc. of "VUJ" mixture. The remaining 3 patients re-

ceived 2.4 gm. in the same volume of "VUJ" mixture. The resulting solution was given intravenously in 3 equally divided doses for 3 consecutive days. One subject received both the high and the low levels of glutamic acid. In 2 of the patients who received the low dose there was a marked decrease in food consumption; 1 vomited violently, the other became nauseated. None of the other subjects developed either anorexia, nausea or vomiting. Thus, it is evident that the depression in food intake may be secondary to the appearance of nausea or vomiting.

Similar observations regarding the influence of aspartic acid upon the voluntary food consumption were made on 3 patients. Each of these patients received 6.3 gm. of aspartic acid dissolved in 1500 cc. of "VUJ" solution. This mixture was given in 3 equally divided infusions for 3 consecutive days. None of these patients showed either a depression of the appetite, nausea or vomiting.

Glutamic and aspartic acids constitute about one-third of the amino acid content of casein. The 2 protein hydrolysates which are most widely employed clinically use casein as the source of protein. These products, therefore, probably have a content of both glutamic and aspartic acids similar to that of casein.\* The present work shows that the amino acid mixture "VUJ" which contains no dicarboxylic acids is better tolerated than any of the glutamic acids containing protein hydrolysates. The hypothesis that glutamic acid and possibly aspartic acid are responsible for the nausea and vomiting in man when protein hydrolysates are given intravenously is supported by the

evidence presented in this report. At the present time, however, the possibility of other factors contributing to the undesirable reactions cannot be excluded. Marked flushing, a common complaint due to rapid intravenous administration of protein hydrolysates, was not noted in the patients who received these dicarboxylic amino acid solutions. This undesirable symptom is probably not due to glutamic and aspartic acids.

It is known that psychologic influences are important factors to consider in evaluating the possible emetic effect of a given substance. In all this work the patients were told that the infusion was part of their general routine therapy and they accepted it as such. No leading questions or undue attention was expressed during the procedure. This eliminates to a large degree the possibility of psychic factors causing the nausea or vomiting.

**Summary and Conclusions.** When glutamic acid dissolved in either the amino acid mixture "VUJ" or water was administered intravenously, nausea or vomiting occurred in 11 out of 17 individuals. Two additional subjects became dizzy.

Aspartic acid was administered under similar conditions to 13 subjects and nausea or vomiting occurred in 4. When the amino acid mixture "VUJ" alone was administered to 9 patients, no undesirable effects occurred.

The probability of the dicarboxylic amino acids being responsible for the decreased tolerance of casein hydrolysates is supported by the evidence presented in this study. However, the possibility of other factors producing nausea and vomiting cannot be excluded.

\* "In 'Parenamine' the approximate value of glutamic acid is 24% and of aspartic acid 6% which is the percentage of these non-essential amino acids in casein." This information was supplied by Earl L. Burbidge, M.D., Frederick Stearns & Co., Inc., Detroit, Mich.

No analytic values for glutamic and aspartic acids in "Amigen" are available according to personal communication from Warren M. Cox, Jr., Ph.D., at Mead Johnson & Co., Evansville, Ind.

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# THE SURVIVAL TIMES OF ADRENALECTOMIZED AND ADRENALECTOMIZED-CASTRATED MALE RATS WITH AND WITHOUT A HIGH SODIUM CHLORIDE INTAKE

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THERE is some overlapping in the biologic properties of the steroid hormones. Testosterone, in addition to certain adrenal cortical and ovarian steroids, has the property of causing some sodium retention.<sup>4</sup> There is a great deal of indirect evidence that the adrenal cortices secrete androgenic substances.<sup>1</sup> Armstrong<sup>2</sup> and Williams *et al.*<sup>5</sup> have found testosterone to benefit patients having adrenal cortical insufficiency. Does the presence or absence of the testis modify the survival times of adrenalectomized animals? Several studies, reviewed by Parkes,<sup>3</sup> have been made of the effect of castration upon the survival times of adrenalectomized animals with negative results.

they ate *ad libitum* during the remainder of the experiment. At the end of 2 weeks on the synthetic diet all of the animals were adrenalectomized by the method of Ingle and Griffith (1942). Asepsis was successfully maintained. Each animal was kept in an individual cage during the remainder of the study. The animals were housed in an air-conditioned room in which the temperature was maintained at 74 to 78° F. and the humidity at 30 to 35% of saturation.

**RESULTS.** Twenty-two pairs of adrenalectomized and adrenalectomized-castrated rats were observed during their survival. All of the animals lost weight rapidly. The non-castrated rats lived an average of 13.6 days, with a range of 6

TABLE 1.—MEDIUM CARBOHYDRATE DIET

Constituent	Gms.	Constituent	Gms.
Cellu flour . . . . .	120	Mazola oil . . . . .	190
Osborne and Mendel salt mixture . . . .	40	Casein . . . . .	160
Dried yeast (Pabst) . . . . .	100	Starch . . . . .	200
Wheat germ oil . . . . .	10	Dextrin . . . . .	190
Cod liver oil . . . . .	10	Sucrose . . . . .	200
Mazola oil plus 100 mg. of vitamin K (2-methyl-1-4-naphthaquinone) . . . .	10	Water to make total volume of 2000 cc.	

The possibility that the favorable effect of a high sodium chloride intake upon the survival of adrenalectomized animals may be affected by the testis has not been studied. We have reexamined the effect of castration upon the survival of adrenalectomized rats and have included animals on both high and low levels of sodium chloride intake. The results were negative.

**Methods.** Male rats of the Sprague-Dawley strain were maintained on Purina Dog Chow until they reached a weight of 300 to 325 gm. At this time 50% of the animals were castrated and all were transferred to a synthetic diet (Table 1) which

to 25 days for individual animals. The castrated animals lived an average of 14.5 days, with a range of 6 to 34 days.

Fifteen pairs of adrenalectomized and adrenalectomized-castrated rats were given 1% sodium chloride solution to drink for 28 days. All of the rats, both castrated and non-castrated, survived this period but either failed to gain weight or lost a few grams. After treatment with saline was withdrawn all of the animals lost weight rapidly and died. The non-castrated rats lived an average of 11.9 days, with a range of 6 to 18 days. The cas-

trated rats lived an average of 15.3 days, with a range of 5 to 35 days.

It can be concluded that the presence of the testis does not favor the survival of the adrenalectomized rat, either with or without treatment with saline.

**Summary.** Twenty-two pairs of adrenalectomized and adrenalectomized-castrated male rats eating a medium carbohydrate diet *ad libitum* survived an

average of 13.6 and 14.5 days respectively. Fifteen pairs of adrenalectomized and adrenalectomized-castrated rats lived for 28 days in apparent "good health" when 1% sodium chloride was added to the drinking water. Following the withdrawal of saline the adrenalectomized rats survived an average of 11.9 days and the adrenalectomized-castrated rats an average of 15.3 days.

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## "TROPIC" ULCERS OF THE HANDS COMPLICATING MYOCARDIAL INFARCTION

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CERTAIN maladies of the shoulder joint, subdeltoid bursa, palmar fascia and finger joints are recognized as sequelæ of myocardial infarction. Although the precise mechanism of these disorders has not been described, most investigators favor the mediation of neurotrophic stimuli from the infarcted ventricle to the cervical dermatomes and metameres coördinated with the cardiac nerves.

Cutaneous lesions, however, have not been described in this connection. Parsonnet<sup>14</sup> has noted herpes zoster of the left hemithorax in close temporal relation to coronary thrombosis; shingles, however, is a distinct entity. It is now possible to record a case in which, promptly after a myocardial infarction, there appeared symmetrical cutaneous vesicles which ruptured to leave deep, slowly healing, painless ulcers of the digits.

**Case Report.** A. B., a 49 year old white man, first noted angina pectoris when he was 41. He suffered his first myocardial infarction in March 1945.

During the night of March 9, 1946, he was stricken with an acute posterior myocardial infarction. The pain was very severe, but like his angina and prior attack, was limited to the chest; at no time had he experienced pain in the hands, arms or shoulders. Two grains of morphine sulfate were required to allay the distress. About 12 hours after the onset, he noted 2 vesicles symmetrically placed over the metacarpophalangeal joints of the index fingers. The thin coverings of these blisters ruptured spontaneously the next day and deeply

punched-out, painless ulcers were left, the right being twice larger than the left (Fig. 1). The escaping fluid was noted as colorless. A coagulum formed quickly in the base of each ulcer; the pink halo of surrounding inflammatory reaction was slight. The ulcers were filled in from below the coagula and from the sides, until after some 10 or 12 weeks only whitish-pink depressed scars remained. At no time in the course of the ulcers was any pain whatsoever experienced. There were no neurologic signs, no thickening of the palmar fascia, no arthritis of the hands, and no evidence of bursitis of the "shoulder syndrome."

The typical electrocardiograms are shown in Figure 2.

**Discussion.** We are of the opinion that the symmetrical ulcers of the hands of the patient reported are the result of the myocardial infarction, and are, therefore, related to the painful shoulders,<sup>2,3,5,9</sup> the disability of the hands,<sup>1,6,11</sup> and Dupuytren's contracture<sup>7</sup> reported in the past decades and now recognized as late complications of the cardiopathy. In the same category, also, are the less well-known phenomena of localized sweating of the chest and arm replacing cardiac pain<sup>4,13</sup> (first noted by Mackenzie<sup>10</sup>), herpes zoster of the thorax in the course of coronary disease,<sup>14</sup> and paroxysmal ocular ptosis with angina.<sup>12</sup>

Various theories have been postulated concerning the mechanism of the involvement of the upper extremities. Libman<sup>9</sup> believed that there was a toxic effect of the ventricular necrosis on joints which were previously sensitized by the "gouty dia-

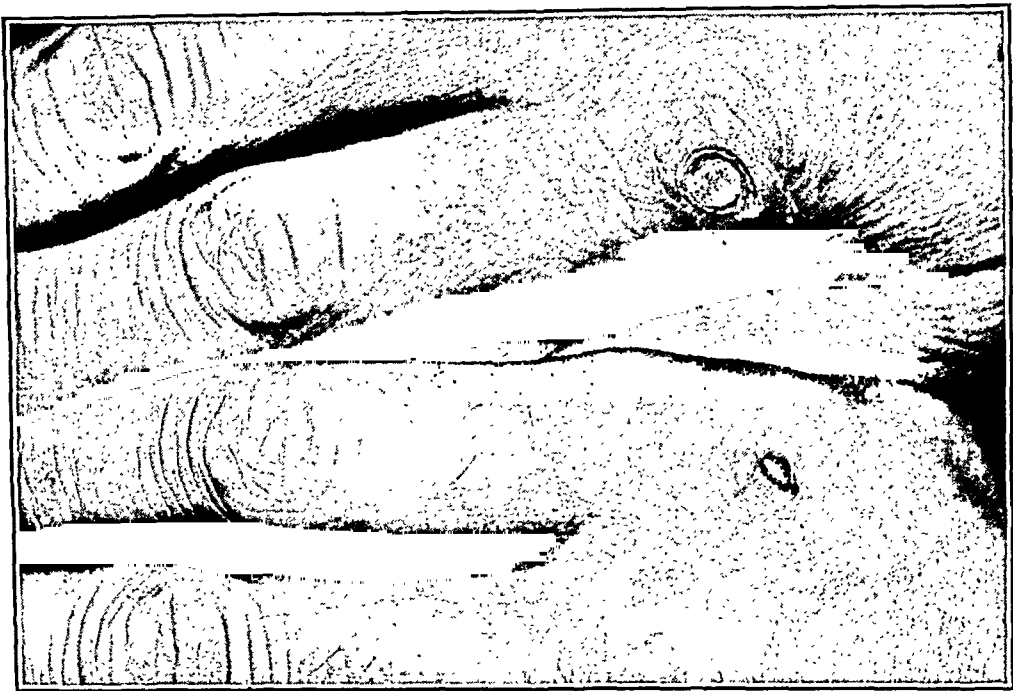


FIG. 1.—Trophic ulcers of the hand.

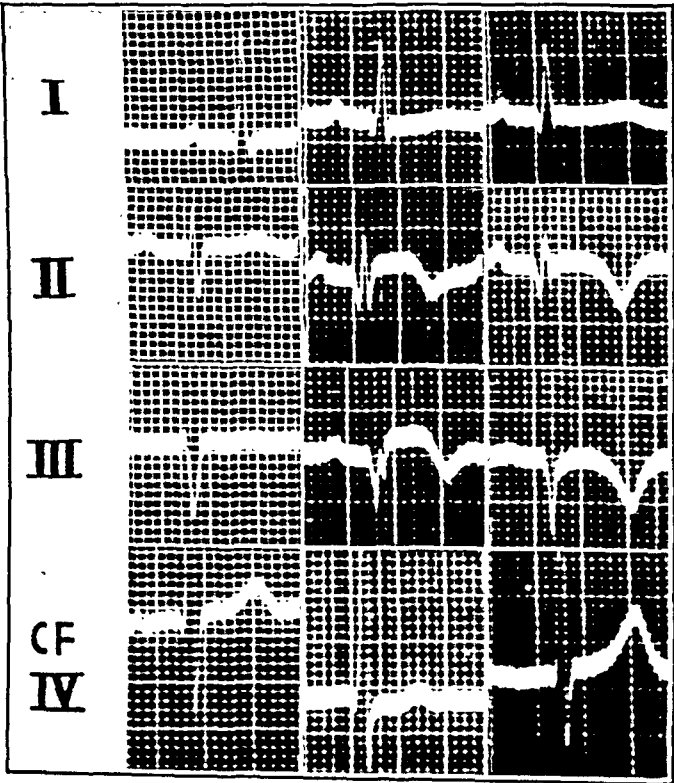


FIG. 2.—Electrocardiograms. A, 8 months before; B, 12 hours after; C, 13 days after the present myocardial infarction.



thesis" or other arthropathy. Boas and Levy discussed the sensitization of a dermatome by another disease. Edeiken and Wolferth<sup>3</sup> suggested an analogy between causalgia and the shoulder syndrome. To Meyer and Binswanger<sup>11</sup> "the possibility of a trophic disturbance following reflex vasomotor changes caused by radiation of the pain down the extremity" seemed most applicable. Johnson<sup>6</sup> was of the opinion that the shoulder and hand syndromes were not related; that the shoulder pain was due to voluntary or involuntary splinting of the shoulder because of "fear of initiating recurrence of the anginal pain and because the shoulder itself is the site of reflex tenderness." The "post-infarction sclerodactylia" he believed due to increased vasoconstriction of the peripheral arteries from pain and fear. Kehl<sup>7</sup> claimed that in Dupuytren's contraction following ventricular infarction "irritation of the sympathetic ganglia" might play an important part. Although Askey<sup>1</sup> noted 2 instances that suggested a predominant rôle of the sympathetic nerves, the majority of his cases seemed to him to be a lighting up of a preëxisting arthritis.

All of the above explanations except Libman's and Johnson's have a common denominator of trophic impulses transmitted from the diseased heart down the areas of cardiac radiation. These speculations leave us with a sense of incomplete explanation, since no provision has been made for the *prompt appearance and ulceration* of the hands as in our case. After reviewing, in this connection, the late Sir Thomas Lewis' investigations on herpes zoster, we believe that while his thesis of antidromic nervous stimulation is not fully proved, it is more acceptable than the other mechanisms mentioned.

Lewis<sup>3</sup> mentioned that Strickler in 1876 learned that the skin of the limb flushed when the cut posterior spinal nerves were stimulated peripherally. Langley later showed that this reaction could be prevented by section of the peripheral sensory nerves and might be produced by the dis-

tal excitation of these fibers. These oft-confirmed experiments proved to Lewis that the nervous impulses "are carried by the sensory nerves antidromically and, ultimately, so it has been supposed, to reach the vessel through sensory nerve off-shoots." Langley, Bayliss and Gaskell independently recognized the incongruity of regarding the antidromic impulse as similar to impulses conducted by vasomotor nerves in general and theorized that the final result of an antidromic reaction might be the liberation of certain metabolites. It remained for Lewis, using Langley's cat's paw preparation, to demonstrate that antidromic vasodilation could be delayed by arresting the circulation to the limb and, therefore, that the flushing was unquestionably due to the liberation of a vasodilator substance.

Lesions identical to herpes zoster may follow invasion of the posterior root ganglion by either malignancy or trauma. Blisters and "trophic" ulcers, likewise, frequently follow injuries of peripheral sensory nerves. Occasionally, herpetiform lesions accompany causalgia. Thus, to use Lewis' words, "herpetic or herpetiform eruptions occur as sequels to lesions of the sensory nerve tracts; not only do they follow irritative lesions of the ganglia, but they are produced also by lesions of those tracts distal to the ganglia themselves."

Lewis and Marvin believed they were unable to reproduce vesicles as the result of experimental antidromic stimulation in animals or man because they could not maintain nerve stimulation over a sufficiently long period.

We return to the unique symptomatology of our case that distinguishes it from the shoulder and hand syndromes previously reported: (1) the prompt appearance, and (2) the vesicle formation and later ulceration of the skin. These may be explained by antidromic stimulation of prodigious degree from the infarcted heart. The fact that our patient was not conscious of pain radiating down his arms during the acute myocardial infarction

(nor, for that matter, during his anginal episodes) fortifies the concept that antidromic impulses are totally different from the usual impulse transmitted centripedally through sensory nerves. It is worthwhile to mention at this point that in the literature quoted the usual shoulder and hand disability appeared in many patients without cardiac pain radiating to the arms or hands.

**Summary.** "Trophic" ulceration of the hands is a rare and apparently hitherto unreported complication of myocardial infarction caused, we believe, by impulses from the infarcted heart mediated antidromically through the sensory nerves.

We suggest that antidromic impulses may be the mechanism of production of the other maladies of the shoulder and hand following myocardial infarction.

We are indebted to Dr. William Dock for many helpful suggestions.

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## PULMONARY VASCULAR LESIONS IN SILICOSIS AND RELATED PATHOLOGIC CHANGES

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THE effect of silicosis on the pulmonary circulatory system and, indirectly, on the right half of the heart constitutes one of the important complications of this disease. Such sequelæ as pulmonary hypertension and right-sided cardiac dilatation, hypertrophy and failure are generally attributed to obliterative vascular changes. However, with the exception of Gerstel's<sup>6</sup> report in 1933, detailed descriptions of the vascular lesions and their pathogenesis are not available in the modern literature. Other workers have described vascular changes briefly in a general description of silicosis or in relation to some other aspect of the pathologic changes. For example, the Coles<sup>2</sup> believed that the dyspnea of silicotic patients was due to obliteration of pulmonary capillaries. Gardner,<sup>4</sup> in a presentation of pneumoconioses of all types, mentioned anemic necrosis as a cause for the irregular slit-like cavities which are found in silicotic fibrous masses. Vorwald<sup>14</sup> also described, among other types of cavitation, a form in conglomerate nodular fibrosis which was considered secondary to interference with blood supply. Riddell<sup>11</sup> reported multiple thromboses of the pulmonary arteries in an interesting case report of silicosis. Policard, Crozier and Martin<sup>9</sup> regarded vascular interference as important in the carnification of pulmonary tissue between silicotic nodules and masses.

The present study was undertaken in an attempt to furnish additional information concerning the nature and evolution of the vascular lesions and to examine as far as possible related changes in the heart and lungs.

**Material and Methods.** The pathologic material was obtained from necropsies performed by the author and from stored specimens collected in the Colorado General Hospital. The series consisted of 45 cases of silicosis. An attempt was made to keep the silicotic series as "pure" as possible; thus, many cases were eliminated because of gross or extensive microscopic evidence of complicating pulmonary tuberculosis. An equal number of fairly normal controls was studied. These cases were unselected and consecutive, except for age, in a series examined postmortem by the author. Since the majority of the silicotic patients in this study were over 50 years of age at the time of death, the controls were taken from a similar age group to eliminate the possible effect of senile "wear and tear" on the pulmonary vessels.

The pulmonary parenchyma and vessels were examined grossly and microscopically. The examinations were made in most cases on sections from the periphery, mid-lung and hilus, so that vessels of all possible dimensions were available for comparative study. Hematoxylin and eosin and Weigert's elastic fiber stains were performed on paraffin blocked tissue prepared in routine fashion. A lesser number of sections was stained by Van Gieson's method for connective tissue, Turnbull's blue method for hemosiderin, and by the scarlet red method for fat. Micro-incineration was performed on the pulmonary sections of 5 silicotic cases.\* At least 80 and often as many as 160 vessels were examined in each case; the average number was about 140. The changes were tabulated according to the size of the vessel: "large" for vessels over 1 mm. in diameter; "medium" over 0.4 mm.; "small" over 0.15 mm.; arterioles, venules and capillaries 0.15 mm. and below.

In grading the degree of silicosis, paren-

\* Micro-incineration was performed through the courtesy of Dr. Henry Yngoda of the National Institute of Health, Bethesda, Md.

chymal changes only were measured. Pleural plaques and isolated fibrosis in peribronchial lymph nodes were not included. The cases were separated into 2 groups: discrete nodular silicosis for lesions varying from 0.2 to 0.5 mm. in diameter and including occasional zones of fibrosis up to 1 cm. in their longest axis; and massive conglomerate nodular silicosis for masses over 1 cm. in their longest axis. Thus, the silicosis in this series was well advanced and corresponded to Grades 2 and 3 by usual roentgenologic standards of classification. This series was made up of 20 cases of discrete nodular and 23 cases of massive conglomerate nodular silicosis.

**Results.** Gross vascular changes were striking in some instances. Extensive arterial thrombosis was encountered in 2 cases of discrete nodular and in 7 cases of massive conglomerate nodular disease. The thrombi were firm, adherent, and in various stages of organization. Occasionally multiple, papillomatous, incompletely occluding, and discontinuous thrombi were found within the main arterial channels in massive conglomerate nodular silicosis. The vessels affected were sometimes encircled by a ring of enlarged hard lymph nodes. Infarcts were not observed. In the large arteries of 8 controls thrombi were found; in all cases they were taken to be embolic and in 7 instances were accompanied by infarcts.

Microscopic examination provided the important information concerning vascular changes. Of all stains used, Weigert's for elastic tissue proved most valuable. To avoid repetition in the text it can be stated here that in discrete nodular silicosis the changes were most marked in small vessels, arterioles, venules and capillaries only. In massive conglomerate nodular involvement vessels of all sizes were affected. Two processes evoked vascular changes: direct encroachment upon the vascular wall by nodules or nodular masses and infiltration by highly cellular dust- and pigment-bearing granulation tissue. The latter advanced irregularly along the margin of the nodule or nodular mass.

**ARTERIES.** *Intima and Lumen.* The direction of movement of infiltrating dust-bearing granulation tissue about affected vessels was from the perivascular region towards the lumen. Before the lumen was reached, however, intimal changes occurred. They began frequently on the encroached side of the vessel. Metaplasia of intimal endothelium to fibroblasts and proliferation of fibroblasts were early reactions which led to intimal thickening (Fig. 1). Later, sprouting capillaries which seemed to arise also from intimal endothelium became visible in the thickened intima. Scattered round cells and pigment particles, usually positive for hemosiderin, were apparent in the stroma of the thickened layer. Elastic tissue stained sections at this stage of the vascular change occasionally revealed thickening of the intimal elastica (Fig. 2). The intimal elastica at all times resisted either encroachment by nodules or infiltration by granulation tissue much longer and much more effectively than did the smooth muscle elements in the adjacent media. However, with prolonged encroachment or infiltration degenerative changes eventually occurred in the intimal elastica. Splitting, unravelling, thinning, pallor and partial disappearance were observed. In some instances hyaline transformation of intimal elastica was noted. All elastic changes were particularly marked in medium and small sized arteries trapped in the centers of conglomerate nodular fibrous masses. Large arteries sometimes revealed degeneration of intimal elastica, as a reaction to encroachment by fibrous hilar masses. Infiltration of the walls of large arteries by dust-bearing granulation tissue was infrequent and penetration of the intimal elastica in this manner uncommon.

Partial or complete occlusion of the lumen occurred from progressive intimal thickening or secondary to the flow of dust-bearing granulation tissue into it. Sometimes a combination of these 2 processes produced occlusion. In occluded vessels many attempts were made to reestablish

circulation by varying sized re-canalizing channels (Fig. 3). Such small channels often continued to function after large segments of the wall of the original vessel had been replaced by fibrous tissue. Occasionally a medium or small artery exhibited surprising resistance to encirclement or invasion by silicotic fibrous tissue and revealed no tendency to reduction in the size of its lumen. Thrombosis in large arteries was described above. Different stages of organization, the majority advanced, were seen but there were no breaks in the vascular wall with secondary invasion of the thrombi by dust-bearing granulation tissue. The pigment within thrombi gave a positive reaction for hemosiderin, whereas pigment within infiltrating granulation tissue was usually negative.

Intimal lipid deposits were considered non-specific and were found as frequently in the normal controls as in the silicotic lungs. Foam cells were numerous and, in zones of extensive lipoidosis, the acicular outlines of crystals were seen. Hyaline changes were present to some degree and were sometimes associated with intimal thickening. Metaplasia and proliferation of intimal endothelium, although observed, were neither as frequent nor as severe as in the silicotic lungs. Scattered calcium deposits were found in the intima of a few large arteries.

*Media.* This layer provided a barrier of smooth muscle to the centripetal movement of dust- and pigment-bearing granulation tissue or to the progressive encroachment, compression or encirclement by nodules or nodular masses. In large

arteries elastic tissue contributed to the barrier and seemed to add to its effectiveness. Increased cellularity in the media was one of the early reactions to injury. The cells were chiefly fibroblasts proliferating *in situ* from "slumbering" mesenchymal cells or arising from metaplasia of smooth muscle cells; also possibly from the endothelium of the vasa vasorum. With prolonged and more direct encroachment of nodules or nodular masses and as infiltration by dust- and pigment-bearing granulation tissue from the adventitia became imminent, the smooth muscle cells disappeared and were replaced by young fibrous tissue (Fig. 4). Round cells were scattered therein and hyperemic vasa vasorum extended inward from the adventitia. Dust- and pigment-bearing granulation tissue soon penetrated the media through single or multiple breaks and streamed down to or through the intimal elastica (Fig. 5).

Although the large arteries sometimes reacted to encroachment and infiltration by thrombosis, they resisted to a better degree, otherwise, than did medium and small sized arteries. Degenerative changes in the muscle and elastic elements, fibrosis and infiltration by granulation tissue were neither as marked nor as frequent.

Non-specific changes found in silicotic and normal lungs included hyaline transformation, calcium deposits and mucoid degeneration. The latter 2 changes, when present, were observed almost exclusively in large arteries.

*Adventitia.* Collars of cellular granulation tissue containing dust and pigment

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FIGS. 1 to 6.

were frequently seen about vessels of all sizes in discrete nodular silicosis. Hyperemia and proliferation of adventitial vasa often accompanied the above and sometimes the vasa were clustered together and they resembled hemangiomas. These changes were noted in small and medium sized arteries in proximity to the margins of nodules; and in large arteries adjacent to silicotic hilar nodes.

In massive conglomerate nodular disease the collars merged with dust-bearing granulation tissue flowing along the margins of encroaching fibrous masses. This fusion ushered in the changes already described in the media and intima (Figs. 6 and 7). Even after occlusion and cessation of function, movement of dust-bearing granulation tissue from adventitia inward continued to disrupt and obliterate the affected vascular wall.

Perivascular fibrosis was seen to a mild degree in many controls. Furthermore, some lungs presented anthracosis with pigment deposits in the perivascular and peribronchial lymphatics.

**VEINS.** Microscopic changes in the various layers were similar to those in the arteries (Figs. 8 and 9). However, the veins offered much less resistance to fibrous encroachment and were occluded at an earlier stage of the silicosis. In hematoxylin and eosin-stained sections of massive conglomerate nodular silicosis veins were absent or difficult to find. They were sometimes visible in elastic stained sections of similar fields but differentiation between medium and small sized arteries and veins was often impossible. In fields where arteries and veins could be distinguished and compared, dilatation and thinning of the wall were more marked in the veins. Pigment-bearing phagocytes were more numerous in the perivascular regions and adventitial and medial layers of the veins than in nearby arteries. Occlusive and disruptive changes were similar, otherwise, to those described in the arteries.

**LYMPHATICS.** In massive conglomerate nodular silicosis the number of lymphatic

channels was greatly reduced, due to destruction and obliteration. Some elastic fragments seen in Weigert's stained sections undoubtedly represented lymphatic remnants though they could not be distinguished from interstitial elements of disrupted pulmonary framework. In discrete nodular silicosis the lymphatics along the margin of nodules often displayed pigmented and hyperplastic endothelium. Obstructed vessels were dilated and their lumens occasionally choked with pigment-bearing phagocytes. Encroachment by nodules sometimes resulted in flattening and distortion of the lumen. Fibrous, hyaline and pigmentary changes were common in the perilymphatic regions. Only rare instances were available in which inward migration of pigment-bearing granulation tissue and occlusion were seen. When either or both of these changes occurred, destruction and disappearance seemed to proceed rapidly and identification of the affected lymphatic vessel was impossible with routine staining methods.

The normal controls showed lymph channels containing pink granular material and an occasional phagocyte. The lungs with some degree of anthracosis revealed pigment in lymphatic intimal endothelium and in the adventitia. Mild hyaline and fibrous transformation were apparent also.

*Small Vascular Channels.* With hematoxylin and eosin stains all silicotic nodules or masses revealed the presence of small thin walled capillaries along their margins. In cross-section the smaller ones were about 20 to 30 microns in diameter, the larger 100 to 150 microns. The functioning channels with erythrocytes in their lumens were oval or round and the lining endothelium unpigmented or slightly so. The non-functioning channels were empty, flattened or cleft-like in configuration and the lining endothelium phagocytic and often heavily pigmented. Artefacts which developed due to shrinkage and separation of laminated fibers could be differentiated as a rule by the absence of lining endothe-

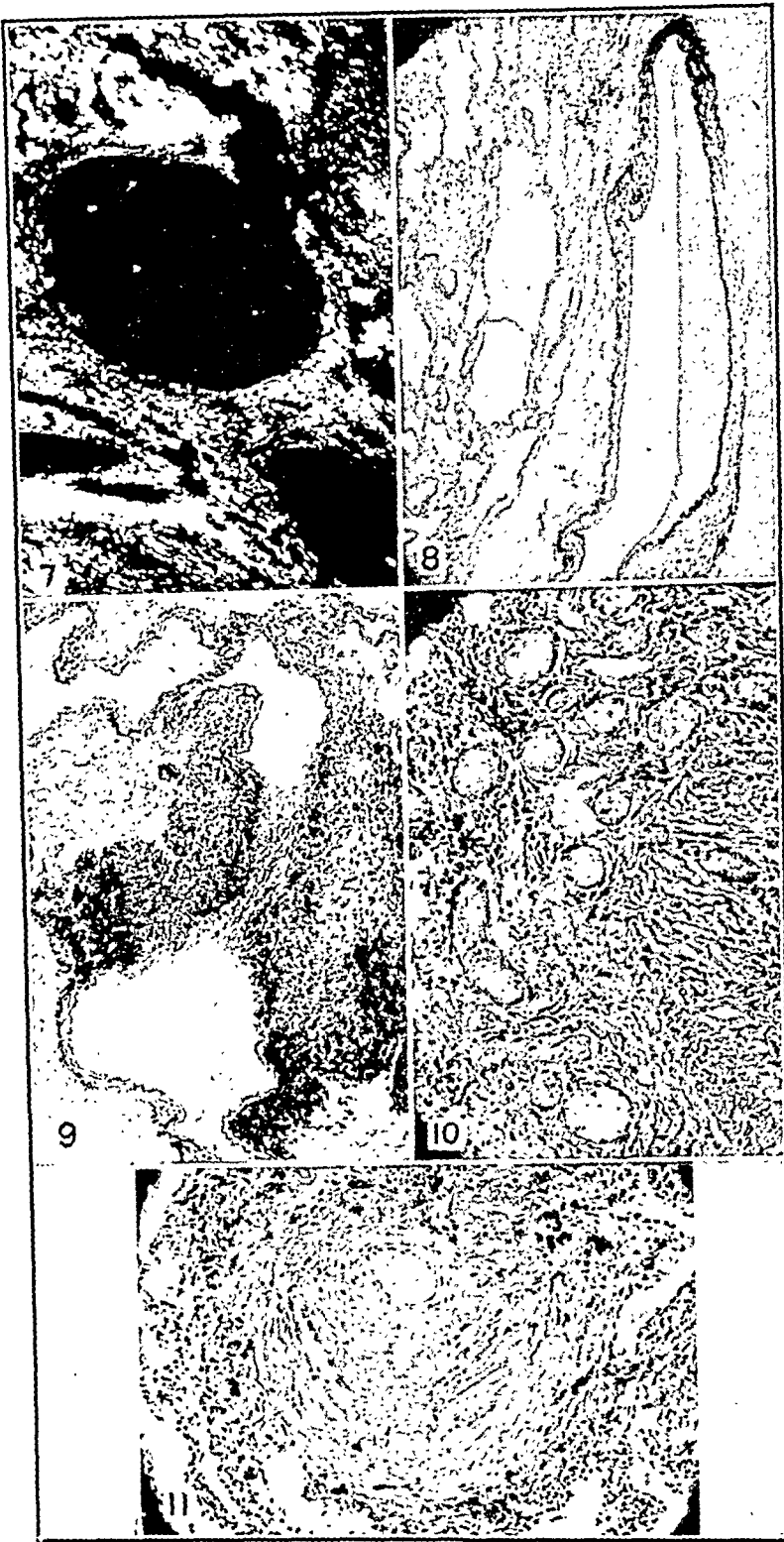


FIG. 7.—Micro-incinerated specimen of same field as in Figure 6. Note arrangement of inorganic ash in wall and compare with Figure 6.  $\times 42$ .

FIG. 8.—Degeneration of part of the wall of a large vein encroached upon by a fibrous silicotic mass (Weigert's stain).  $\times 21$ .

FIG. 9.—Constriction of a medium sized vein by pigment-bearing granulation tissue (Weigert's stain).  $\times 33$ .

FIG. 10.—Dilated thin-walled capillaries in the margin of a conglomerate nodular mass (hematoxylin and eosin).  $\times 111$ .

FIG. 11.—Patent arteriole near the center of a typical silicotic nodule (hematoxylin and eosin).  $\times 93$ .



lium. As one moved the microscopic field from the margin of a nodule or nodular mass towards the center, a progressive decrease first in small functioning channels and then in the non-functioning cleft-like capillaries was observed. In the center some of the irregular, fragmented and pigment-bearing clefts represented disrupted vascular channels, but with hematoxylin and eosin stains it was impossible to differentiate them from artefacts. Viability of the lining endothelium in the non-functioning cleft-like capillaries suggested that, for a time at least, the cells were kept alive by some type of serum circulation, either through the lumen or by diffusion from without. Free pigment was often present in their lumens indicating rupture of cells containing pigment at some other level.

Necrotic areas in the centers of massive conglomerate nodular silicosis were often completely acellular and consisted of unorganized material: anthracotic pigment particles, calcium granules, the acicular outlines of crystals, and occasional poorly stained "ghost" cells in a crumbling, fragmented and, in parts, porous stroma. Occasional strands of hyaline fibrous tissue supporting empty vessels projected inward. Weigert's stain for elastic tissue demonstrated large numbers of obliterated or partly destroyed vessels from medium sized arteries and veins down to arterioles, venules and capillaries. Unidentified and disorganized elastic fiber remnants were visible also. All changes were much more striking than in the hematoxylin and eosin stained sections and one gained the impression of an extensive "turn-over" in small channels. Many were obliterated within nodular masses but new capillaries sprouted constantly along the margins in a futile effort to maintain circulation (Fig. 10). In some fields necrosis seemed directly related to the distance of the necrotic zone from functioning vascular channels.

In many small typical silicotic nodules a functioning arteriole could be seen in or near the center. The engulfed vessel

seemed to have provided a focus for the nodule (Fig. 11). Such a vascularized lesion resembled the experimental silicotic nodule described by Gardner<sup>5</sup> and varied from the typical nodule in human silicosis.

**RELATED PATHOLOGIC CHANGES IN THE HEART.** The clinical course of the patients with conglomerate nodular silicosis in this study was often aggravated by progressive cardiac disability. Furthermore, dilatation and hypertrophy of the right side of the heart and other anatomic evidence of cardiac failure were frequently encountered at necropsy. Table 1 reveals, however, that most patients were in their 7th or 8th decades at the time of death. Thus careful examination of the heart was essential to rule out contributing degenerative diseases, particularly hypertensive cardiac hypertrophy and severe coronary arteriosclerosis with or without occlusion. Table 2 indicates the thickness of the right ventricle in the 3 groups. Of the 20 cases in the discrete nodular silicotic group, 10 hearts revealed right ventricular thickness of 0.5 cm. or more. In the conglomerate nodular group slightly more than three-fourths, 16 out of 23, showed similar hypertrophy. The thickest right ventricle was encountered in the latter group and measured 1.3 cm. Of the 43 normal pulmonary controls 5 hearts revealed right ventricular hypertrophy. Ten cases in the discrete nodular and 4 in the conglomerate nodular silicotic series, or a total of 14, revealed moderate or severe arteriosclerosis. Thirty-four cases in the controls showed the same change. Two cases in the discrete nodular and 1 in the conglomerate nodular series revealed cardiac hypertrophy due to systemic hypertension. Eight cases in the controls showed this cardiac change. One case of valvular heart disease, aortic stenosis, was found in the silicotic series; 4 cases of valvular heart disease were encountered in the controls.

A summary of clinical and necropsy evidence of cardiac failure is given in Table 3. Seven patients in the discrete nodular group had evidence of a cardiac

disability which was of major importance as a cause of death. However, in all but 1 case pathologic cardiac changes unrelated to silicosis were found to be responsible. Thus despite the presence of right ventricular hypertrophy to 0.5 cm. and more in 10 out of 20 cases of discrete nodular silicosis, only 1 case was found in which right-sided heart failure was of major etiologic importance in the terminal illness. In that case right-sided cardiac dilatation and failure were encountered secondary to massive bilateral pulmonary arterial thrombosis. The right ventricle in this instance was 0.4 cm. in thickness.

ventricular wall was only 0.3 cm. in thickness. Thus in slightly less than half of the cases of massive conglomerate nodular silicosis (11 out of 23) right-sided heart failure was of major importance as a cause of death.

Twelve patients in the control group had evidence of a major cardiac disability on final entry to the hospital. Coronary occlusion with myocardial infarction, bacterial endocarditis, hypertensive heart disease with decompensation and rheumatic heart disease with decompensation were most common in the above order of frequency. In the 5 patients with right ven-

TABLE 1.—AGE DISTRIBUTION

	No. cases	41-50	51-60	61-70	71-80	81 and over
Discrete nodular silicosis . . . . .	20	0	3	7	7	3
Conglomerate nodular silicosis . . . . .	23	1	5	13	4	0
Normal controls . . . . .	43	0	5	15	21	2

TABLE 2.—CARDIAC CHANGES AT NECROPSY

	No. cases	Thickness of right ventricle		Other cardiac lesions			
		Normal	0.5 cm. and over	Coronary A.S. (mod. or severe)	L. hypertens. hypertrophy	Valvular H.D.	
Discrete nodular silicosis . . . . .	20	10	10	10	2	1	
Conglomerate nodular silicosis . . . . .	23	7	16	4	1	0	
Normal controls . . . . .	43	38	5	34	8	4	

TABLE 3.—CLINICAL AND NECROPSY EVIDENCE OF CARDIAC FAILURE

	No. cases	Clinical			Necropsy			
		Cyanosis	Peripheral edema	Dyspnea	Pulmonary edema	Hydrothorax over 200 cc. on either side	Ascites 200 cc. or more	Chr. p.c. internal organs
Discrete nodular silicosis . . . . .	20	7	5	12	8	7	3	13
Conglomerate nodular silicosis . . . . .	23	16	10	17	9	9	6	18
Normal controls . . . . .	43	8	9	18	13	13	4	23

Thirteen patients in the massive conglomerate nodular silicotic group had evidence of a cardiac disability of major importance. In addition to the tabulated evidence, electrocardiograms in these cases usually showed varying degrees of right axis deviation. The only significant pathologic cardiac change in 10 cases was right ventricular hypertrophy with varying degrees of dilatation. Cardiac changes unrelated to silicosis were found in 2 cases. In the other, right-sided cardiac dilatation and failure were observed but the right

tricular thickness of 0.5 cm. or more, systemic hypertensive heart disease with failure was found twice. Rheumatic mitral valvular heart disease with failure and coronary occlusion with myocardial infarction were encountered once each. Death was due to trauma (automobile accident) in the fifth case.

RELATED PATHOLOGIC CHANGES IN THE LUNGS. The centers of the black firm masses of conglomerate nodular silicosis often contained varying sized areas of necrosis. In some instances a gentle

stream of water across the freshly cut surface was sufficient to wash away necrotic debris and to outline or create a zone of cavitation. The typical cavities of ischemic necrosis were small, narrow, multiple and sometimes coalescent. Less typical lesions were circular or irregular in contour. All types contained serum heavily colored by anthracotic pigment. After this was washed away, a lining layer of moist gritty black semisolid matter was revealed. The walls were black, fairly firm and merged imperceptibly with the adjacent fibrous tissue of the mass. The cavities in this series varied from 0.2 to 3.5 cm. in their longest axis and were found in 7 patients out of 23 in the conglomerate nodular group. No communication with bronchi could be demonstrated. The reports of chest roentgenograms were inconclusive in most cases. Cavitation was sometimes suspected but even with heavy penetration the diagnosis was indefinite.

Microscopically, this lesion revealed walls composed of crumbling amorphous material supported in part by strands or layers of fibrous tissue. Calcium granules, the outlines of crystals, anthracotic pigment, free or within degenerated phagocytes, and "ghost" cells were visible. The fibrous strands and adjoining layers were mainly avascular or contained non-functioning, partly degenerated vessels. Their lumens were often filled with pigmented granulation tissue. Occasionally, in larger cavities, functioning vascular channels were found in some fields of the wall. Living cells, as manifested by staining qualities, were visible also in such fields and the wall appeared more discrete and firm. Crystals were less numerous or absent.

In 2 other patients in the conglomerate nodular group cavities up to 3.4 cm. in their longest axis were observed. These lesions were irregular in shape and were lined by grayish yellow crumbling material superimposed on fibrous walls. Microscopically, the surface matter proved to be an exudate made up of fibrin, plasma

cells, lymphocytes, macrophages, polymorphs, scattered clumps of bacteria and cellular debris. The concentration of cells in the exudate varied in different sections. The adjacent fibrous walls also showed variability in the concentration of cellular infiltrates: Some fields were acellular and relatively avascular. Others revealed infiltration to plasma cells and lymphocytes among proliferating capillaries, fibroblasts and epithelioid cells. Giant cells were not encountered. This lesion was believed to be tuberculous with its morphology modified, in part by progressive ischemia, also possibly by other factors inherent in silica inhalation.

Pseudocavities were sometimes found in emphysematous areas. Although vascular lesions had no bearing on their development, brief mention will be made of points of differentiation from ischemic cavities. Whereas ischemic cavities were present in or near the centers of fibrous masses, these lesions were located along the margins of the masses. Most often they were encountered between the visceral pleura and the mass, particularly in the upper lobes. The walls of the pseudocavity were sometimes fairly thick, fibrous and black, always thicker and firmer than ordinary blebs or bullae. Microscopically, the lesion exhibited a wall composed of pigmented, hyalinized, fibrosed and compressed parenchyma except in the portion which abutted on the conglomerate nodular mass. Vascularization was much better than in the wall of the typical cavity of ischemic necrosis. The lining was irregular and contained edema fluid and occasional polymorphs. The development of pseudocavities was believed related to contraction of the silicotic fibrous mass with disruption of marginal alveoli. Hyperinflation secondary to bronchial and bronchiolar changes was also considered important.

The rôle of vascular changes in stimulating pulmonary fibrosis was difficult to evaluate because many other factors were important also. Infarction was not observed. Coalescence of typical nodules

to form the large masses of advanced silicosis was brought about in a background of subacute or chronic inflammation. The changes important in coalescence were: gradual increase in size of the nodules, proliferation of hyperemic, highly cellular granulation tissue along nodule margins and pathologic alteration in the intervening pulmonary parenchyma. Among the factors which were involved in effecting the latter change were atelectasis, in turn the result of bronchiolar compression and obliteration; and contraction of silicotic nodules with stretching, twisting and disruption of adjoining alveolar walls. Vascular congestion was apparent in the alveolar walls and edema fluid, "heart failure" phagocytes and, less often, fibrin deposits were visible within the alveolar lumens. Lymph stasis was indicated by the presence of degenerating, dust-bearing phagocytes, closely packed within distended alveoli. Plasma cells and lymphocytes were numerous in both the proliferating hyperemic granulation tissue and in the intervening pulmonary parenchyma. Polymorphs were present in occasional foci but were not as concentrated as the round cells. Although vascular obliteration and destruction were often marked in the margins of this pulmonary "battleground," the effect of the reduced blood supply in preparing the intervening pulmonary parenchyma for fibrous conversion could only be surmised.

**Comment.** Observations in this study indicated wide individual variability in vascular resistance to the infiltrative, disruptive and obliterative effects of silicosis. Many vessels revealed unobstructed lumens though completely surrounded by silicotic fibrous tissue. Others remained patent despite partial or complete replacement of the wall by invading granulation tissue. However, this does not deny that functional disturbance resulted in the circulation through such vessels due to interference with distensibility.

Although massive conglomerate nodular silicosis often shortened life, it is interesting to note that of the 23 cases in

that group, 13 patients were in their 7th decade of life and 4 in the 8th decade at the time of death (Table 1). It should be reemphasized, however, that tuberculosis was largely excluded in this study.

Occlusion, disruption and obliteration, as described in the text, were observed frequently in massive conglomerate nodular silicosis. The outstanding processes which operated to bring this about were: encroachment by expanding nodules and infiltration by dust-bearing granulation tissue. Vascular lesions appeared to evolve rapidly and extensively in massive conglomerate nodular disease with but little preliminary changes in the discrete stage. Small vessels and capillaries mainly were involved in discrete nodular silicosis and the changes appeared self-limited with little tendency to extent beyond the nodule.

Intravascular pressure changes were believed to be important factors also in pathogenesis. Gerstl<sup>6</sup> regarded the changing pressure during normal pulsation as significant in injuring vessels surrounded or fixed at various points by fibrous masses. If this view is correct, then traumatic effects should be more severe under the influence of increased pulmonary intra-arterial pressure. This often occurs in massive conglomerate nodular silicosis due to elimination of large portions of the pulmonary vascular bed and interference with distensibility of the remaining channels. Recently Cournand, Bloomfield, Lauson and co-workers reported a method for recording the pressure in the right auricle and ventricle in man by venous catheterization. Although their series<sup>1</sup> contained only 3 cases of silicosis, they were able to detect the existence of pulmonary arterial hypertension in 2. In his comprehensive review on the genesis of arteriosclerosis Hueper<sup>7</sup> called attention to the resultant anoxemia of the vascular wall when increased intravascular hydrostatic pressure compressed the vasa vasorum. Anoxemia due to interference with vasal circulation was believed to result also from the marked perivascular fibrous

changes in massive conglomerate nodular silicosis. Adventitial vasa hyperemia and proliferation as described in this study probably represented a reaction to interference with vasa circulation and an attempt to establish collateral channels.

Evaluation of the degree of right-sided cardiac dilatation was hampered by the lack of a suitable standard for guidance and comparison. Furthermore, in hearts with marked dilatation, right-sided hypertrophy was sometimes obscured because the wall was thinned. In such cases thickened columnae carneae, enlarged pectinate and papillary muscles and deep intervening recesses were suggestive of hypertrophy, but the ventricular thickness by routine measurement was normal. In 2 patients with right-sided cardiac failure the right ventricular thickness was only 0.4 cm. or less. More exact methods of measurement are available but are not used in routine necropsy work because they are too time-consuming. For example, dissection of the right and left ventricular walls and independent weighing for comparison are far more accurate than measurement of thickness only, at one or possibly two points. In a consideration of right and left ventricular size which was independent of the main report<sup>10</sup> on postmortem coronary arterial injection and Roentgen ray, Ravin and I contemplated the possibility of cutting out right and left ventricular areas from a paper copy of the roentgenogram. Further studies on a series of 166 hearts will be the basis for a future report on relative right and left ventricular size. The total number of cases of right ventricular hypertrophy in this series was 26 out of 43 cases (60%). This conforms with the results of Coggin, Griggs and Stilson<sup>3</sup> who found an incidence of 58% in a series of 102 cases.

In an experimental study, Visscher<sup>12</sup> found that acute elevation of right atrial or ventricular pressure in the isolated dog heart was followed by ventricular fibrillation and failure. Elevation of pressure on the left side was comparatively well tolerated. He explained the deleterious

effects on the basis of decrease in the coronary vascular pressure gradient: The coronary venous sinus empties into the right auricle. Furthermore, the right circumflex artery which applies most of the right ventricle drains almost exclusively, 92% on the average, into the right side of the heart through the right thebesian system; whereas the left cardiac thebesian flow is much less: about 1%. Increased pulmonary arterial pressure and increased right ventricular work are reflected in the high incidence of right ventricular hypertrophy in this series of silicotic patients. The increase in pulmonary arterial pressure is probably slowly progressive over many years and differs in this respect from the acute studies described above.<sup>13</sup> The heart is able to compensate by hypertrophy and increased work for some time. However, in massive conglomerate nodular disease right-sided cardiac failure frequently supervenes. It was regarded as of major importance as a cause of death in 11 out of 23 patients in that group.

Many complex factors operated to bring about central necrosis in discrete or massive conglomerate nodular silicosis. In discrete nodular disease the death of cells appeared to be related to the age of the lesion, prolonged intimate contact with free silica, proliferation of fibroblasts, progressive deposition of collagenous fibers and disruption of nourishing capillaries. Some of these factors were interrelated: thus the older the lesion, the longer the exposure of trapped cells to silica dust. Necrosis of capillary endothelium and capillary disruption probably resulted also from the direct toxic action of silica. In older silicotic nodules compression and obliteration of small vascular channels occurred due to contraction of the basket-weave arranged fibers. Despite varying degrees of central necrosis, discrete nodular silicosis in many cases in this series seemed self-limited or healed. The clinical history in some patients indicated exposure for relatively short periods many years previously. Cavitation was not

observed in the discrete nodular form of the disease.

Obliteration and disruption of many large and medium sized vessels introduced the factor of ischemia on a more important scale in massive conglomerate nodular silicosis. Furthermore, the effects of some of the other mentioned factors were multiplied. It must be emphasized again that in this series tuberculosis was largely eliminated and its rôle in inducing necrotic changes will be mentioned only.

Gardner<sup>4</sup> described cavities of anemic necrosis as small and slit-like within fibrous masses and such small lesions are probably the best examples. However, larger cavities have been recognized in recent years. Vorwald<sup>14</sup> described a few which involved a large portion of a lobe. McCloskey<sup>8</sup> reported large cavities on this basis with lesions measuring 5 and 7 cm. in diameter in the upper lobes. In this series the cavities of ischemic necrosis varied from 0.2 to 3.5 cm. in their longest axis; they were found in 7 patients out of the 23 in the massive conglomerate nodular group.

**Summary.** 1. The pulmonary vascular lesions and related pathologic changes were studied in 43 cases of silicosis. Cases with complicating pulmonary tuberculosis were largely excluded. A similar series of 43 non-silicotic patients in the same age group was used as controls.

2. Two morphologic processes seemed to evoke vascular changes: direct encroachment on the vascular wall by nodules or nodular masses and infiltration of the vascular wall by dust- and pigment-bearing granulation tissue.

3. In discrete nodular silicosis the vascular lesions were not striking, as a rule, and were found only in small arteries, small veins, arterioles, venules and capillaries. In massive conglomerate nodular silicosis the vascular lesions were severe, were found in vessels of all sizes and were demonstrable best in sections stained for elastic fibers.

4. Fibroblastic proliferation was an early reaction in all layers of the arterial wall; later, proliferation of vasa and

capillary channels and degeneration of muscle and elastic tissue occurred. Occlusion and disruption of the vascular wall by infiltrating granulation tissue which streamed through all the layers were end-results. Thrombosis of large arteries was observed in 2 cases of discrete nodular and in 7 cases of massive conglomerate nodular silicosis.

5. The veins revealed similar occlusive and disruptive changes but appeared to offer less resistance than the arteries. Lymphatic vessels often showed distention, stasis and endothelial pigmentation. In massive conglomerate nodular silicosis veins and lymphatics were often destroyed without trace.

6. Related pathologic changes in the heart included right ventricular hypertrophy to a thickness of 0.5 cm. or more at necropsy in 10 out of 20 cases in the discrete nodular group and 16 out of 23 cases in the massive conglomerate nodular group. Although 7 patients in the discrete nodular group had clinical and necropsy evidence of a cardiac disability which was of major importance as a cause of death, only 1 instance was found in which the right-sided cardiac changes alone were responsible. Thirteen of 23 patients in the massive conglomerate nodular group had clinical and necropsy evidence of a major cardiac disability. In 10 hearts of this group right ventricular hypertrophy and varying degrees of dilatation were the only significant changes. One case showed right-sided cardiac dilatation without increased thickness. Right-sided cardiac failure was considered to be the cause of death in 11 out of 23 cases in the massive conglomerate nodular group.

7. Related pathologic changes in the pulmonary parenchyma (namely, fibrosis, ischemic necrosis and ischemic cavitation) were described. Ischemic cavitation was found in the fibrous masses of 7 patients in the conglomerate nodular group. Pseudocavitation due to emphysema was sometimes encountered.

8. The rôle of pulmonary intravascular pressure changes in producing vascular injury was discussed.

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# EFFECT OF ANTIHISTAMINIC SUBSTANCES ON THE EDEMA PRODUCED BY EGG WHITE IN THE RAT

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THE therapeutic use of antihistaminic substances has been based upon their effectiveness in preventing conditions (histamine shock, anaphylactic shock, peptone shock) which do not resemble allergic manifestations.<sup>4,6,8,9</sup> Recently, an anaphylactoid reaction resembling angioneurotic edema has been described in the rat.<sup>7</sup> This experimental reaction induced by egg white furnishes a close parallel to certain human allergies and offers an opportunity to transpose into human pathology the therapeutic measures used in the treatment of this experimental condition. The present investigation has been conducted to determine the effect of various antihistaminic substances on the edema produced by egg white in the rat.

**MATERIAL AND METHODS.** Male albino rats (130) of 80 to 100 gm. in weight were divided into 13 groups of 10 animals each. Animals of Groups I to IV received 10, 7, 4 and 2 mg., respectively, of 2-(N-phenyl-N-benzyl-aminomethyl)-imidazolin or "Antistine"; those of Groups V to VIII received 10, 7, 4 and 2 mg., respectively, of  $\beta$ -dimethyl-amino-ethyl-benzhydryl ether or "Benadryl", and those of Group IX to XII, 10, 7, 4 and 2 mg., respectively, of N-p-methoxybenzyl-N-dimethyl-aminoethyl- $\alpha$ -aminopyridine or "Néo-antergan". These substances, in water solution, were injected subcutaneously; each dose was contained in 0.4 cc. of liquid. Animals of Group XIII were kept as controls. Half an hour after the administration of the antihistaminic compounds, all the rats received 1 intraperitoneal injection of a solution of powdered egg white equivalent to 0.15 cc. of fresh material.

This powder came from the same batch of lyophilized fresh egg white. Two hours later, the animals were examined for signs of edema on the face and paws; the degree of the edema was recorded according to a scale of 0 to ++++. The results are summarized in Table 1, where the incidence and the severity of edema are expressed as a per cent of the maximum possible.

The data reveal that the threshold of activity of "Antistine", "Benadryl" and "Néo-antergan" is approximately 10, 4 and 4 mg., respectively. All the animals injected with 10 mg., and part of those injected with 7 mg., of "Benadryl" and "Néo-antergan" presented signs of hyperexcitability (violent excitement, convulsions, ataxia), followed by a secondary depression. Respiratory failure and death occurred in some animals receiving the larger doses. These signs contrast with those found in man which consist of sedation, drowsiness, muscular aching, pelvic heaviness and mild nausea.<sup>2,10,12</sup> A few days after the injections, we observed in some animals, especially in those on high dose levels, ulcerations in the area of injections subsequent to local necrosis. This confirms previous observations made by Mayer *et al.*,<sup>10</sup> who attributed the effect to the local anesthetic properties of the antihistaminic substances.

Although it has already been demonstrated that antihistaminic substances have a very short duration of action, we investigated the possible effect of "Benadryl" on subsequent injections of egg white. Rats, which received a dose of "Benadryl" sufficient to inhibit the edema



reaction, were given, as well as controls, the following day the same dose of egg white. All the animals reacted the same way: incidence of 100% for both groups and intensity of 53% for the "Benadryl"-treated rats and 50% for the controls. "Benadryl" has therefore no effect on the sensitivity of egg white injected in subsequent days.

The only reference found regarding "Antistine" indicates only that it prevents anaphylactic shock in rabbit.<sup>13</sup> In the test based on the protection from lethal intravenous doses of histamine, "Neo-antergan" is approximately 25 times more active than "Benadryl".<sup>5</sup> Preliminary studies<sup>5</sup> indicate on the other hand that the difference in the antianaphylactic

TABLE 1.—EFFECT OF VARIOUS ANTIHISTAMINIC SUBSTANCES ON THE EDEMA CAUSED BY EGG WHITE IN THE RAT

Group	Compound	Doses in mg.	Response*	Incidence %	Intensity %
I	Antistine	10	0(9), + - + + (1)	10	5
II	"	7	0(6), + (3), + - + + (1)	40	15
III	"	4	0(5), + (2), + - + + (3)	50	22
IV	"	2	0(3), 0 - + (1), + (2), + - + + (1), + + - + + + (1), + + + (1)	70	38
V	Benadryl	10	0(10)	0	0
VI	"	7	0(10)	0	0
VII	"	4	0(8), + (1), + - + + (1)	20	8
VIII	"	2	0(4), 0 - + (3), + (1), + - + + (1), + + (1)	60	20
IX	Néo-antergan	10	0(10)	0	0
X	"	7	0(10)	0	0
XI	"	4	0(8), + (1), + + (1)	20	10
XII	"	2	0(3), 0 - + (1), + (1), + - + + (2), + + (2)	70	33
XIII	....	..	0(2), 0 - + (4), + (1), + - + + (1), + + (2)	80	25

\* Edema of face and paws recorded according to a scale of 0 to + + +.

The number of animals giving the same response is indicated in brackets.

In connection with this study, it was of interest to ascertain whether "Néo-antergan" was detoxified by the liver or eliminated through the kidney. For this purpose, partially hepatectomized rats and completely nephrectomized rats were injected with a dose (4 mg.) of "Neo-antergan" just insufficient to produce toxic symptoms. If one of the above-mentioned organs played a rôle, there would be accumulation of antihistaminic substances in the organism to the point where the animals would present signs of excitability and convulsions. This experiment showed that the partially hepatectomized and the completely nephrectomized rats behaved like normal animals receiving the same dose of "Néo-antergan." It can be assumed that it is detoxified at its points of attack, that is, in all the tissues.

**Discussion.** Lack of information prevents us from comparing accurately the ratio of potency of the 3 antihistaminic drugs as measured in the egg white edema test with that obtained with other tests.

activity of the 2 compounds is not as great as that shown against histamine shock. This observation is in agreement with the results obtained by our method, since "Benadryl" and "Néo-antergan" are equally potent in preventing the formation of edema.

Although the present investigations tend to demonstrate that histamine is responsible for the formation of egg white edema, it must be pointed out that the rat is very resistant to histamine and to anaphylactic shock; the lethal dose of histamine is about 500 mg. per kg. and anaphylactic shock is rarely fatal under the best experimental conditions.<sup>3</sup> This would indicate that there is no necessary correlation between general and local sensitivity. Another example is found in the mouse which is highly resistant to histamine, but which can develop severe anaphylactic shock. In this connection, it is interesting to note that Mayer and Brousseau<sup>14</sup> found that, although antihistaminic substances are effective in anaphylactic shock in mice,

they are not antagonists, but synergists of histamine. Similar experiments which we performed with "Néo-antergan" showed that in the rat, on the other hand, this compound at the dose of 70 mg. per kg. alleviated symptoms elicited by intravenous or intraperitoneal injections of 250 mg. per kg. of histamine and prevented formation of appendicitis, as described by Selye.<sup>15</sup> Without contesting the fact that antihistaminic substances may, under certain conditions, possess opposite pharmacologic activities, it must be kept in mind that antihistaminic drugs and histamine at high dose level are toxic, so that the increased death rate of the animals could be the result of summated toxicities.

It is interesting to note that the antihistaminic drugs are especially effective in relieving the symptoms of angioneurotic edema, a condition which resembles

the experimentally produced egg white edema.<sup>1,2,9,12,14</sup> We have no direct proof that histamine-release plays a rôle in the egg white edema. However, since the antihistaminic drugs inhibit this response, the possibility has to be considered. In any event, the test for the ability of antihistaminic drugs to inhibit the egg white reaction would appear useful as an additional index for their effectiveness in counteracting the angioneurotic edema, whatever their pathogenesis may be.

**Summary.** The edema produced in the rat by intraperitoneal injection of egg white can be inhibited by antihistaminic drugs. Although there is no direct proof that this edema is due to a local release of histamine, it appears that the test for the ability of antihistaminic drugs to inhibit the egg white reaction would be useful as an additional index for their effectiveness against similar conditions.

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## CONSTITUTIONAL REACTIONS AND MACULÆ CERULÆÆ ATTENDING PHTHIRIASIS PUBIS

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To our knowledge, there has been no published evidence that the pubic louse may produce febrile reactions caused by toxins introduced by its bite. As pointed out by Jamieson,<sup>3</sup> the peculiar pigmentation described as *maculæ cerulææ* has been associated with pubic lice since the year 1868 when the relationship was discovered by Falot and Moursou. Jamieson also came to consider these lesions pathognomonic of *Phthiriasis pubis* and cited 3 cases of *maculæ cerulææ* associated with different febrile diseases. He clearly indicated the confusion which might result from such coincidences. These lesions, associated with the local annoyance attending such infestations, particularly in individuals having thin, light colored skin, occur as pea- to dime-sized grayish blue stains over the chest, abdomen, thighs and upper arms. They do not fade on pressure and are believed to be due to some reaction of the host to the parasite. Duguet,<sup>1</sup> by his studies in 1880, including inoculation with the juice of crushed pediculi, believed that he demonstrated that the lesions arise from the subcutaneous deposition of pigment occurring in the body of the parasite. Inoculation of heated extracts of the lice produce no reaction.<sup>2</sup> Montgomery<sup>5</sup> believes that these lesions are the direct result of the action of the saliva of the pediculi on the hemoglobin of the host turning it green. This occurs in the small hemorrhages situated in the skin and appears as bluish pigmentations shining through the horny layer. Histologic studies have shown no cause for the pigmentation. Moore<sup>4</sup> re-

ported a febrile illness accompanied by chills, a rash and symptoms very similar to "grip" occurring in himself and associate while allowing 700 to 800 "clothes lice" (*Pediculus corporis*) to feed on their arms. He suggested that these constitutional symptoms were due to a toxin, or toxins, introduced by the bite of the body louse.

The difficulty in differential diagnosis on the admission of patients presenting such an association of symptoms and signs can be readily appreciated when one considers the gamut of diseases to be eliminated in the etiology of fevers of undetermined origin. Recently we were confronted with 2 such patients occasioning sufficient difficulty in diagnosis and speculation in etiology to warrant reporting.

**Case Reports.** CASE 1. C. R., a 20 year old white single male, entered the hospital July 17, 1946, 18 days after discharge from the U. S. Army, complaining of pain in the right chest of 4 days duration. The patient had been in excellent health until July 12, when he noted a purulent urethral discharge and dysuria, coming on 2 days after sexual exposure. The following day, a private physician made a diagnosis of gonorrhea without a smear of the discharge and over a 3 day period gave the patient 160,000 units of penicillin. This was followed by the disappearance of the urethral discharge and dysuria on the 2nd day of therapy. The chest pain, beginning suddenly during the day of July 13, involved the entire right anterior hemithorax, radiating to the right shoulder, and was typically pleuritic in nature. On July 14, the patient experienced a true rigor followed by a subjective sensa-

tion of fever, sweating and right frontoparietal headache, the latter persisting until admission to the hospital. Within 24 hours general malaise became prominent. Nausea and vomiting of greenish fluid occurred twice. For 4 days prior to admission, anorexia was evident and mild non-productive cough was present. With the persistence of these symptoms he was sent to the hospital by his private physician with a tentative diagnosis of "rheumatism" and venereal disease. His past history was non-contributory and there was no history of previous parasitic infestations.

The patient was a well-developed, well-nourished, decidedly blond youth who appeared to be moderately but acutely ill. His skin was of normal texture, flushed, moist and was covered with a vast number of adherent, yellowish or grayish specks which on microscopic examination proved to be *Pediculosis pubis*. There were numerous pea- to dime-sized, grayish macules with a steel-gray tint, distributed over the chest, abdomen, buttocks, thighs and upper arms. These lesions did not disappear on pressure. Many nits were demonstrable on the pubic hairs about  $\frac{1}{2}$  inch above the skin and rust-colored or reddish specks of excrement could be seen. There was considerable excoriation of the skin from scratching. His eyes, ears, nose, mouth and pharynx revealed no abnormality. Heavy percussion over the right anterior rib cage and the right upper quadrant of the abdomen produced local discomfort. The lungs were clear to percussion and auscultation; no friction sound was heard at any time. A short, soft, Grade I, apical systolic murmur was the only abnormality found on examination of the heart. The remainder of the examination showed no abnormality.

The temperature was 101° F. and the pulse was 80 per minute on admission, the former rising to 103° F. that evening. It then subsided in an irregular steplike descent to normal on the 7th hospital day. The pulse exhibited a relative bradycardia through most of the febrile period. The white blood cell count on admission was 12,700, of which 77% were polymorphonuclears, 21% lymphocytes, 1% eosinophils and 1% monocytes. The red blood cell count and hemoglobin determination were well within normal limits. On 2 occasions the urine revealed only an occasional pus cell. The white blood cell

count progressed as follows: July 18, 17,250; July 19, 16,000, with the differential essentially unchanged; July 20, 10,900 with 70% polymorphonuclear cells, 16% lymphocytes, 9% monocytes, 4% eosinophils and 1% basophils.

On July 17, blood culture was negative and blood urea nitrogen was 16 mg. per 100 cc. On admission the chest Roentgen ray revealed clear lung fields as did a repeat examination on July 19. The Widal reaction was positive at a dilution of 1 to 320 and *B. paratyphosus* B was agglutinated up to 1 to 160. (The patient had received typhoid-paratyphoid vaccine in the army, the last immunization was in August 1945.) Agglutination of the patient's serum against *B. paratyphosus* A, Salmonella group and *Brucella abortus* was negative. The heterophil agglutination reaction was reported positive only through a dilution of 1 to 16. The Weil-Felix reaction was negative on July 23. Repeated blood cultures were negative. Sputum culture yielded no pneumococci. The blood icterus index was 5 and the cephalin flocculation test was 1+ in 48 hours. Blood Kahn was negative on July 17, on July 22 and again on August 8.

The patient received no specific therapy except general hygienic measures and the application of 10% thymol in olive oil for the pediculosis. On the 6th hospital day he was asymptomatic and was discharged on the 9th hospital day. The lice could no longer be seen; although somewhat faded, the maculæ were still recognizable.

CASE 2. R. N., a 15 year old white male farm-hand from a nearby rural village, was sent by his local physician to the contagious division of the Cincinnati General Hospital on July 27, 1946, with a tentative diagnosis of poliomyelitis.

The patient related a history of excellent health until 3 days prior to admission, when he awoke with aching, stiffness and weakness of both lower extremities. In the next 24 hours, lassitude, anorexia, chilly sensations and subjective sensations of fever became prominent in the order named. On his initial visit to his family physician, July 25, the temperature was 102.6°. He was given undetermined oral medication without alleviation of symptoms. Intermittent, throbbing, frontal headache and an occasional mild hacking cough were admitted on questioning. Except for several loose stools

following an enema the day before hospitalization, the patient had been constipated since the onset of his illness.

On the farm, horses furnished his only direct animal contact. For 12 days prior to admission, he had been swimming in a local creek. His drinking water was derived from a well on the farm. Approximately 1 week prior to admission, he had picked 2 non-engorged, apparently unattached ticks off of his head. As far as could be ascertained, there had been no other cutaneous parasitism prior to his present infestation with lice.

His past history was non-contributory except for an acute inflammatory process in the right knee at the age of 9 years.

The patient was a well-developed, well-nourished lad appearing mildly but acutely ill. On admission his temperature was 102.8° F., pulse 76 per minute and respirations normal. The face was flushed. He was blond and had a thin, light colored skin. In the hair of the pubis, axillæ, abdomen and extremities numerous nits and a vast number of lice were seen. Over the chest, abdomen, buttocks, thighs and arms numerous typical maculæ ceruleæ were found. The bulbar and palpebral conjunctivæ were moderately injected. The upper pole of the left tonsil showed a mild vascular injection. The tonsillar nodes were enlarged and the posterior cervical chain of lymph nodes was palpable bilaterally, the left being larger than the right and was slightly tender. There were small, palpable right axillary nodes and barely palpable inguinal nodes. The examination of the heart was marked by a blowing, Grade III, systolic murmur, most intense at the base and less so at the apex, transmitted as far as the mid-axilla. Tenderness was elicited on compression of the left trapezius muscle. Spinal fluid examination in the receiving ward of the contagious disease section revealed no abnormality.

On admission to the medical service, the red blood cell count was 4,800,000 per c.mm.; the hemoglobin was 14.5 gm. per 100 cc. The leukocytes numbered 8400, with 74% polymorphonuclears, 25% lymphocytes and 1% monocytes. On July 31, the leukocyte count was 9200, and on August 2, the leukocytes numbered 8600, with 58% polymorphonuclears, 34% lymphocytes, 3% monocytes, 4% eosinophils and 1% basophils. No abnormal cells were observed.

Urinalysis was negative except for approximately 1 granular cast per high power field. The spinal fluid exhibited no abnormalities. On July 27, blood culture and blood Kahn were negative. Serum agglutination for *Bacillus typhosus* and *Brucella abortus* was negative on July 27 and August 5. Agglutination against the heterophil antigen was negative on July 31 and August 5. No pathogens were cultured from the stool on 3 successive days. The cephalin flocculation test was negative in 24 hours, 1+ in 48 hours. On August 5, blood specimens were sent to the National Institute of Health, Bethesda, Md., and complement fixation tests for endemic typhus and Rocky Mountain spotted fever and agglutination tests of the patient's serum against *B. proteus* OX-19 were reported as negative.

Microscopic examination of several of the parasites showed them to be 0.5 to 0.1 mm. in length, with their breadth almost equal to their length. The thorax and abdomen were not divided and the heads of these lice were seated squarely on the body. Eight teat-shaped feet terminating in pointed claws were attached to the margin of the abdomen. These parasites were of grayish yellow color and were more or less translucent.

On July 28, biopsy of one of the pigmented skin lesions was taken. Microscopic sections were reported as follows: "Microscopic examination shows an essentially normal epidermis and corium. An occasional cell (chromatophore) laden with brown pigment granules is present in the papillary corium. There are no evidences of inflammation."

On the basis of these findings, a diagnosis of *Phthiriasis pubis* was made. The patient was treated with general hygienic measures and Cuprex (Merck), a copper salt in an organic solvent, was applied daily to all hairy portions of the body. The temperature subsided and was normal in 24 hours. The patient was free from symptoms of disease. At the end of the 2nd hospital day, however, the temperature began to rise and reached a maximum of 101° F. During the course of reexamination of the patient at this time, a large number of pediculi were found covering the lumbar back and buttocks. These had escaped detection and treatment. The parasites in these areas were promptly eliminated. On the evening of the 3rd hospital day the temperature returned to normal where it remained throughout his hospital

stay. All lice and nits had disappeared by the time of his discharge, free from symptoms of disease, on the 10th day. The maculæ ceruleæ had faded by the 7th day.

**Summary.** 1. Two cases are reported showing moderately severe constitutional reactions and maculæ ceruleæ accompanying massive infestation with pubic lice.

2. Both cases were hospitalized with

tentative diagnosis of more serious import and presenting all the problems in differentiation of fever of obscure origin.

3. Rapid and complete recovery followed eradication of the parasites.

4. The possibility of an acute febrile illness resulting from toxins introduced by the bite of pubic lice, as suggested by these 2 cases, deserves consideration.

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# PROGRESS OF MEDICAL SCIENCE

## **PATHOLOGY AND BACTERIOLOGY**

UNDER THE CHARGE OF

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### **THE STATE OF THE ARTERIOLES IN ESSENTIAL HYPERTENSION**

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IN an attempt to clarify the relation between hypertension and arteriolar sclerosis, many investigators have studied the state of the arterioles in the organs and tissues of hypertensive patients. Most of these studies have been devoted to the qualitative aspects of the histologic changes in the arterioles, but this review will deal mainly with the results of the relatively small number of investigations in which the arteriolosclerotic process has been studied by more or less quantitative methods. The histologic grading of degrees of severity of a complex process such as arteriolosclerosis must obviously depend on the use of arbitrary criteria, therefore the data obtained by this method of study are only semi-quantitative, although the results are of definite comparative value as long as the criteria are clearly stated and uniformly applied to any one investigation.

**Methods of Study.** Several authors have tried to compensate for the subjective element in the grading of arteriolar sclerosis by measuring the dimensions of representative samples of the arterioles in

various organs and tissues, the most widely used method being that of Kernohan, Anderson and Keith.<sup>20</sup> In this technique, 2 measurements of the diameter of the lumen (L) and 4 measurements of the width of the arteriolar wall (W) are made on 5 to 10 arterioles in tissue sections prepared and stained by standard methods. Unfortunately, Kernohan, Anderson and Keith reported their measurements in terms of the "lumen/wall ratio" (L/W); therefore, their published results, and those of other authors who have adopted their technique, do not usually give any direct information on the average size of the lumen of the arterioles, since low values of L/W may be due to an increase in the value of W with or without a simultaneous decrease in the value of L.

In evaluating the significance of such measurements, allowance must be made for variations in arteriolar dimensions caused by postmortem contraction of the vessels and by shrinkage of tissue during fixation. For example, MacWilliam and Mackie<sup>27</sup> found that these sources of error may cause variations of 25 to 100 % in the

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width of the lumen and as much as 30 % in the thickness of the media of arteries, while Andrus<sup>1</sup> and Lisa, Eckstein and Solomon<sup>24</sup> came to the conclusion that the discrepancies are so large and unpredictable that measurements on fixed material are practically valueless. Moritz and Oldt,<sup>29</sup> working with the arterioles of skeletal muscle, found that errors due to wide variations in histologic technique were no greater than those involved in the use of the measuring micrometer, but they were of the opinion that the overall precision of the technique was too low to allow much reliance to be placed on data based on measurements of 5 to 10 arterioles in each section. However, in spite of the obvious validity of these criticisms, it is probable that some of the sources of error tend to neutralize each other, since the figures obtained by different authors who have used the Kernohan technique agree surprisingly well, not only with each other, but also with the results of Moritz and Oldt, which were based on the measurement of 75 arterioles in each section.

The dimensions of the arteriolar bed may also be studied by injection methods which involve the use of radio-opaque solutions as described by Graham,<sup>12</sup> and others. This method provides an excellent means of studying the architectural pattern of the vascular tree, but the neoprene injection-corrosion technique of Duff and More<sup>7</sup> seems to offer a more satisfactory method of making accurate measurements of the width of the lumen of individual arterioles. Only preliminary studies have been reported with this technique, but much valuable information will undoubtedly be obtained by the wider application of this method to the study of the arteriolar bed of the kidney and other organs of hypertensive patients.

**The Histologic Characteristics of Arteriolar Sclerosis.** Most authors agree that arteriolosclerosis is a composite process which involves the simultaneous occurrence of one or more of a number of different pathologic changes in the arteriolar wall. The individual components of

the arteriolosclerotic process include intimal hyalinization, collagenous intimal thickening, elastic intimal hyperplasia, endothelial hyperplasia, medial hypertrophy, medial degeneration, adventitial fibrosis, productive endarteritis and necrotizing arteriolitis. The characteristics of some of these processes, such as intimal hyalinization and elastic intimal hyperplasia, are accepted by all observers, but there are still considerable differences of opinion regarding the frequency of occurrence of some of the other components of the arteriolosclerotic process. For example, many authors do not recognize hyperplasia of smooth muscle cells as a common feature of arteriolar sclerosis, while even those who are convinced of its existence admit that true medial hyperplasia cannot always be differentiated from the artefact produced by postmortem contraction of the vessel wall. A similar difference of opinion exists in regard to endothelial hyperplasia, but productive endarteritis and necrotizing arteriolitis are widely recognized as the characteristic lesions of the renal end-stage of so-called "malignant" hypertension.

The highly variable appearance of the lesions which may be classified under the general heading of arteriolosclerosis is due partly to normal variations in the structure of the walls of arterioles of different sizes, partly to differences which are characteristic of the arterioles in various organs and tissues, and partly to variations in the severity and duration of the hypertensive process in different patients. It is inevitable, therefore, that attempts to grade the severity of arteriolosclerosis will be subject to relatively large errors, and this must be borne in mind in evaluating the data presented below.

**THE RENAL ARTERIOLES.** (a) *Quantitative Grading of Arteriolar Sclerosis.* The most important semi-quantitative studies of the incidence and severity of renal arteriolosclerosis in hypertensive patients are those of Bell and Clawson<sup>3</sup> (1928), Moritz and Oldt<sup>29</sup> (1937), Castleman and Smithwick<sup>5</sup> (1943), and Bell<sup>2</sup> (1946).



Bell and Clawson<sup>3</sup> studied autopsy material from 420 hypertensive patients, and graded the degree of renal arteriolosclerosis in 368 cases as slight, moderate or severe, on the basis of the amount of subendothelial hyalinization. These authors restrict the term "arteriole" to the afferent glomerular arterioles only, and they make no mention of other changes such as medial hypertrophy and endothelial hyperplasia. The average age of the patients in this series was about 56 years.

Bell<sup>2</sup> has recently reported a much larger series based on a study of autopsy material from 1180 hypertensive patients and 449 controls. The degree of arteriolosclerosis was graded separately in the "arterioles" (afferent glomerular arterioles) and "pre-arterioles" (terminal portions of the interlobular arteries) on the basis of intimal changes only. Four grades of severity were distinguished, namely: 0, 1, 2, and 3, as well as a subgroup of grade 1 which was called 1p to indicate that the intimal involvement was partial rather than diffuse. Excluding those cases in which the diagnosis of essential hypertension was not fully established, results are given for 500 hypertensive patients who died of causes other than renal failure, and for 309 non-hypertensive controls. The average age of the hypertensive patients in this series was about 58, and the average age of the controls about 68 years.

Moritz and Oldt<sup>29</sup> studied autopsy material from 100 hypertensive patients and 100 non-hypertensive controls matched for age, sex and race. They used the term "arteriole" to include the afferent glomerular arterioles and the terminal branches of the interlobular arteries up to an outside diameter of 100 microns, and they graded the severity of the arteriolosclerotic process as mild, moderate or severe, on the basis of a composite assessment of subendothelial hyalinization, medial hypertrophy and endothelial hyperplasia. The average age

of the patients in this series was about 53 years.

Castleman and Smithwick<sup>5</sup> studied small biopsies of the renal cortex obtained from 100 hypertensive patients who were subjected to the operation of lumbodorsal sympathectomy. Their grading of arteriolar sclerosis was based on the evaluation of intimal hyalinization, medial hypertrophy and endothelial hyperplasia in vessels up to a maximum outside diameter of 100 microns. They reported their results in five grades (0, 1, 2, 3, and 4), but from their description it seems likely that their grades 3 and 4 are roughly comparable to the grade 3 of other authors who have used the 0-3 system. The results of Castleman and Smithwick are of special interest from the clinical point of view because the average age of their patients was only 40 years as compared with 53 to 58 years for the 3 autopsy series. The validity of the biopsy method has been severely criticized by Goldblatt,<sup>10</sup> because of the small amount of tissue available for examination, but there is no reason to suppose that the admittedly large sampling error of the technique would be more likely to lead to an underestimation than to an overestimation of the degree of arteriolar sclerosis. In any event, the fact that the biopsy method is open to a certain amount of justifiable criticism should not be given undue weight, since the data summarized in Table 1 show that the results of the biopsy study are in essential agreement with the results of other investigations which involved the use of autopsy material.

The data presented in Table 1, as well as the results of other investigators who have studied the problem,<sup>8,15</sup> show that organic changes in the renal arterioles are present in almost every case of hypertension, but the complete absence of renal arteriolosclerosis in a small percentage of cases is an equally clear-cut finding which must not be ignored in the formulation of any hypothesis which seeks to explain the exact nature of the relation between hypertension and renal arteriolosclerosis.

(b) *The Size of the Lumen of the Renal Arterioles.* A common error in the interpretation of findings such as those presented in Table 1 is the assumption that the presence of even the least severe grades of renal arteriosclerosis implies the existence of a significant degree of mechanical obstruction of the renal circulation. This tendency to ignore the quantitative aspects of the problem has been criticized by Kimmelstiel and Wilson,<sup>21</sup> and the validity of this criticism would seem to be upheld by the fact that the literature contains surprisingly few reports

the thickness of the wall, although it is a matter of common observation that narrowing of the lumen and increase in the thickness of the wall of the renal arterioles are both frequently present in the kidneys of hypertensive patients. However, several authors including Löhlein<sup>25</sup> (1917), Jaffé<sup>17</sup> (1925), Fishberg<sup>2a</sup> (1925), and Moritz and Oldt<sup>29</sup> (1937) have described dilatation of the afferent glomerular arterioles as one of the characteristic features of the renal vascular bed in the earlier stages of hypertension. This somewhat surprising observation does not seem to have attracted

TABLE 1.—INCIDENCE AND SEVERITY OF ARTERIOLAR DISEASE IN THE KIDNEYS OF HYPERTENSIVE AND NON-HYPERTENSIVE PATIENTS

Author	Type of material	Number	Average age	Grade of Arteriolosclerosis		
				None (per cent)	Slight and moderate (per cent)	Severe (per cent)
<i>Hypertensive Patients</i>						
Bell and Clawson <sup>3</sup> . . . . .	Autopsy	368	56	10.6	44.5	44.9
Moritz and Oldt <sup>29</sup> . . . . .	Autopsy	100	53	3	50	47
Castleman and Smithwick <sup>5</sup> . . . . .	Biopsy	100	40	7	46	47
Bell <sup>2</sup> . . . . .	Autopsy	500	58	17.5	50.9	31.6
<i>Non-hypertensive Controls</i>						
Bell and Clawson <sup>3</sup> . . . . .	Autopsy	—	—	—	—	—
Moritz and Oldt <sup>29</sup> . . . . .	Autopsy	100	53	88	12	0
Castleman and Smithwick <sup>5</sup> . . . . .	Biopsy	—	—	—	—	—
Bell <sup>2</sup> . . . . .	Autopsy	309	68	52	47.4	0.6

TABLE 2.—MEASUREMENTS OF THE ARTERIOLES IN THE KIDNEYS OF HYPERTENSIVE PATIENTS

Authors	No. of patients	Type of hypertension	L/W*
Pilcher and Schwab <sup>33</sup>	6	Controls	2.11
	15	Essential	1.13
Cain <sup>4</sup>	9	Controls	1.83
	27	Malignant	0.63
Foa <i>et al.</i> <sup>9</sup>	13	Essential	0.61

\* Ratio of arteriolar lumen to width of wall.

of actual measurements of the degree of narrowing of the arterioles in the kidneys of hypertensive patients, especially in the early stages of the disease.

The results obtained by 3 groups of investigators who employed the Kernohan technique are shown in Table 2, but the only conclusion which can be drawn from these limited studies is that the L/W ratio of the renal arterioles of hypertensive patients seems to be reduced to about one-half the normal value. Unfortunately, none of the authors gave separate figures for the diameter of the lumen and

much attention, although Bell and Clawson<sup>3</sup> state that dilatation of the afferent arterioles was rarely observed in their material.

Another interesting description of the characteristics of the vascular bed in the kidneys of hypertensive patients has been given by McMahon<sup>26</sup> on the basis of careful measurements on 100 kidneys from normal and hypertensive patients. He noted that in normal kidneys the lumen of the vascular channels decreased very gradually as one passed from the arteries into the arterioles, while in hypertensive

kidneys the rate of decrease in the size of the lumen was much more rapid. He interpreted his findings as evidence of the occurrence of a relative dilatation of the arteries and a relative constriction of the arterioles in the hypertensive kidneys. A somewhat similar picture of the general architecture of the vascular system of hypertensive kidneys was obtained by the radiographic injection technique of Graham,<sup>12</sup> but the neoprene injection-corrosion technique of Duff and More<sup>7</sup> would seem to be the method of choice for future studies of this aspect of the renal circulation.

(c) *Changes in the Juxta-glomerular Apparatus.* A brief consideration of the possible significance of the juxta-glomerular apparatus in the pathogenesis of hypertension is relevant to the present discussion because Goormaghtigh<sup>11</sup> and others believe that this structure exercises a measure of control over the renal circulation. According to Goormaghtigh<sup>11</sup> the juxta-glomerular apparatus consists of a group of specialized afibrillar smooth muscle cells which are situated in the walls of the afferent arterioles close to their point of entrance into the glomerulus. A characteristic feature of the cells of the juxta-glomerular apparatus is the presence of granules which can be seen in sections stained by Masson's trichrome method, although the ease with which these granules can be demonstrated varies greatly from one species to another. On the basis of extensive studies of the behavior of the juxta-glomerular apparatus in experimental renal hypertension, Goormaghtigh has evolved the hypothesis that these cells constitute an endocrine organ whose function is to secrete renin, and thereby to initiate the renin-hypertensinogen-hypertensin pressor mechanism. Although Goormaghtigh himself has made only preliminary observations on human kidneys, Kaufmann<sup>18</sup> has studied the juxta-glomerular apparatus in the kidneys of 400 patients, and has found evidence of hyperplasia of the afibrillar cells in the renal arterioles of hypertensive patients. Oberling,<sup>31</sup> on the

other hand, who also studied the juxta-glomerular apparatus in several hundred human kidneys, came to the conclusion that the characteristic lesion in hypertensive patients is not hyperplasia but degeneration of the afibrillar cells. As a result of this observation, Oberling has modified Goormaghtigh's hypothesis by postulating that the juxta-glomerular apparatus normally exerts a depressor effect, which is reduced or eliminated in hypertensive patients. However, Castleman and Smithwick<sup>5</sup> were unable to confirm the observations of either Kaufmann or Oberling, since they did not detect any significant changes in the juxta-glomerular apparatus in renal biopsies from 100 hypertensive patients. It is evident, therefore, that much further investigation is required before Goormaghtigh's interesting hypothesis can be accepted as having direct applicability to the pathogenesis of essential hypertension in the human.

(d) *The Relation of Renal Arteriosclerosis to Hypertension.* The close correlation between renal arteriosclerosis and hypertension has given rise to three schools of thought regarding the possible cause and effect relation between the two conditions, namely, (1) that hypertension is the sole cause of arteriosclerosis, (2) that arteriosclerosis is an "aging" process which may affect many organs, but which causes hypertension only when it involves the kidney, and (3) that hypertension and arteriosclerosis are independent processes which often undergo parallel development, and are capable of intensifying one another in the later stages of their evolution. The first of these views is clearly untenable, because typical instances of renal arteriosclerosis are encountered in non-hypertensive patients. Moritz and Oldt<sup>29</sup> and Goldblatt<sup>10</sup> are the principal proponents of the second hypothesis, which is based on the belief that the pathogenesis of essential hypertension is similar to that of experimental renal hypertension in animals. The existence of a small percentage of hypertensive patients in whom no renal arteriosclerosis

can be demonstrated is explained by Moritz and Oldt on the assumption that renal ischemia in these patients is caused by arteriosclerosis of the larger renal arteries, although Yuile,<sup>36</sup> in a recent review of the evidence on this subject, came to the conclusion that arteriosclerotic narrowing of the main renal artery must be considered one of the very rare causes of hypertension. Moreover, the occurrence of renal arteriosclerosis in the absence of hypertension constitutes another serious objection to the acceptance of the Goldblatt hypothesis, although Moritz and Oldt have sought to explain this finding by making the additional assumption that renal arteriosclerosis does not cause hypertension except in the presence of certain other unknown factors, which are presumably absent in those individuals with renal arteriosclerosis who do not have hypertension. Moreover, even if these explanations are accepted at their face value, most observers find it difficult to believe that any but the more severe degrees of arteriosclerosis can cause sufficient renal ischemia to produce hypertension by the Goldblatt mechanism. Since there is no reliable method of calculating the degree of impairment of renal circulation which corresponds to any observed degree of renal arteriosclerosis, the acceptance or rejection of the Goldblatt theory depends on differences in the interpretation of the functional significance of the observed pathologic changes, rather than on any serious disagreement as to the validity of the general conclusions drawn from a consideration of the results of studies such as those summarized in Table 1. However, in the absence of clear-cut physiologic evidence of the occurrence of significant degrees of renal ischemia in the early stages of essential hypertension, the majority opinion in the literature at the present time appears to have rejected the second hypothesis in favor of the third, which represents a compromise between the two extreme views.

The idea that renal arteriosclerosis and

hypertension are independent processes in the earlier stages of their development has been most clearly enunciated by Kimmelstiel and Wilson<sup>21</sup> and by Bell,<sup>2</sup> although both of these authorities believe that hypertension and renal arteriosclerosis are capable of intensifying one another in the later stages of their development. In conclusion, it should be emphasized that the acceptance of this hypothesis does not imply a complete rejection of the possibility that the pathogenesis of hypertension may originate in some functional disturbance of the renal circulation. The crux of the argument is merely that the adherents of the third hypothesis do not believe that this circulatory disturbance can reasonably be attributed to simple mechanical obstruction of the renal circulation by the relatively mild arteriosclerotic lesions which are so often observed in the kidneys of hypertensive patients in the early stages of the disease.

**THE ARTERIOLES OF SKELETAL MUSCLE.** The state of the arterioles in skeletal muscle has been studied by several authors, not only because this tissue contains such a large fraction of the total arteriolar bed of the body, but also because of the ease with which samples of muscle can be obtained by biopsy. Table 3 presents a summary of the results obtained by 6 investigators who have made measurements of the L/W ratio of the arterioles in skeletal muscle by the Kernohan technique.

In spite of the difficulties caused by the use of different classifications of hypertension and different definitions of the term "arteriole," there is surprisingly close agreement between the figures reported by different authors. Apparently the normal L/W ratio of the arterioles of skeletal muscle is about 2.0, while in patients with moderately severe hypertension the ratio falls to about 1.4, and in the most severe cases to about 1.0. However, the results of the two studies in which separate figures are given for L and W suggest that the observed

decrease in the L/W ratio is due mainly to an increase in the thickness of the wall rather than to a decrease in the diameter of the lumen. On the basis of these findings, Foa, Foa and Peet<sup>9</sup> conclude that medial hypertrophy is the characteristic response of the arterioles of skeletal muscle to the stresses caused by the increased intravascular pressure, although Fishberg<sup>8</sup> did not observe medial hypertrophy in the arterioles in skeletal muscle in 72 patients with essential hypertension, and Andrus<sup>1</sup> reported only fibrotic changes in the media in his series of 32 cases. It

skeletal muscle. In spite of the obvious incompleteness of the available data, a few tentative conclusions may be made regarding the incidence of arteriolosclerosis in various parts of the body.

(a) *Gastro-intestinal Tract, Liver, Pancreas, Adrenal.* In general, the changes in the arterioles in these abdominal viscera are similar to those which occur in the kidney, but the distinction between the hypertensive and control groups is not as clear-cut, because there is a somewhat higher incidence of mild degrees of arteriolar sclerosis in the controls, and a some-

TABLE 3.—SUMMARY OF RESULTS OF MEASUREMENTS ON THE ARTERIOLES OF SKELETAL MUSCLE

Author	Material	No. of patients	Type of hypertension*	Size of arterioles ( $\mu$ )	L/W	L( $\mu$ )	W( $\mu$ )
Kernohan <i>et al.</i> <sup>20</sup>	Biopsy	50	Controls	25-100	2.0		
	"	11	Benign		1.4		
	"	18	Severe benign				
	"	23	Malignant		1.1		
Moritz and Oldt <sup>29</sup>	Autopsy	38	Controls	18-72	1.9	15.4	8.4
	"	38	Essential		1.4	15.8	11.3
Keith <i>et al.</i> <sup>19</sup>	Biopsy	50	Controls	25-100	2.0		
	"	10	Grade I		1.7		
	"	26	Grade II		1.3		
	"	37	Grade III		1.3		
	"	65	Grade IV		1.2		
Odel <sup>32</sup>	Autopsy	58	Controls	25-100	1.9	21	11
	"	20	Grade IV		1.2	19	15
Heyer and Keeton <sup>16</sup>	Biopsy	14	Controls	25-100	2.0		
	"	14	Essential		1.4		
	"	5	Malignant		1.0		
	"	4	Acute nephritis		1.9		
	"	8	Chronic nephritis		1.1		
Foa <i>et al.</i> <sup>9</sup>	"	8	Miscellaneous	25-100	1.4		
	Biopsy	36	Controls		1.8†		
	"	350	All grades		0.9		

\* Grades used in this column are those of the Keith-Wagener classification.

† These figures were calculated from the data shown in Figure 1 of the paper of Foa *et al.*, because the figures given in the text were calculated on a different basis from that used by the other authors whose results are listed in Table 2.

is also of interest that Graybiel, Allen and White<sup>14</sup> failed to demonstrate the expected difference in the L/W ratio in the arterioles of biopsy specimens of skeletal muscle taken from the arms and legs of 5 patients with coarctation of the aorta who had a moderate degree of hypertension confined to the upper extremities.

**THE ARTERIOLES IN OTHER ORGANS AND TISSUES.** Table 4 presents a summary of the relatively small amount of data which has been obtained by the application of quantitative or semi-quantitative methods of study of tissues other than kidney and

what lower incidence in the hypertensives, especially in the liver. The measurements on the arterioles of these 4 viscera show that the L/W ratio decreases in proportion to the severity of the hypertensive state to about the same extent as in skeletal muscle (Table 3), the decrease in the ratio being due to simultaneous reduction in the diameter of the lumen and increase in the thickness of the wall. The pancreas and the adrenal are also mentioned by several authors as the commonest sites, apart from the kidney, for the occurrence of



hypertensive patients is less striking than in the other abdominal viscera.

(c) *The Heart and Lungs.* The qualitative studies of Moritz and Oldt<sup>29</sup> as well as the measurements reported by Odel<sup>32</sup> and Pilcher and Schwab<sup>33</sup> show that the arterioles of the myocardium are seldom affected by significant degrees of arteriolosclerosis. It is doubtful whether the 10% increase in the thickness of the wall of the arterioles in Odel's series can be considered significant in view of the known experimental error of the Kernohan technique. All observers agree that the arterioles of the pulmonary vascular bed are not affected in hypertension which is confined to the systemic circulation.

(d) *The Brain.* The measurements made by Rosenberg<sup>34</sup> on the arterioles of the brain call attention to the wide lumen and thin wall which is characteristic of the normal cerebral arterioles, but his figures also show that there is a definite decrease in the lumen and an increase in the thickness of the wall in hypertensive patients. The data of Moritz and Oldt<sup>29</sup> show that the incidence of arteriolosclerotic changes in the cerebral arterioles in an unselected group of hypertensive patients is about the same as in the liver, but Davison and Brill<sup>6</sup> observed widespread and severe arteriolosclerosis in the cerebral arterioles of hypertensive patients in whom cerebral symptoms were the predominant manifestations.

(e) *Retina and Choroid.* In view of the widespread use of the ophthalmoscopic examination of the retinal vessels as an index of the severity of the vascular disease in hypertensive patients, it is surprising that the literature contains so few detailed studies of the pathologic changes in the retinal arterioles. Greear<sup>43</sup> has recently reviewed the literature on this subject and has correlated the ophthalmoscopic appearance of the retina with the pathologic findings in a series of 16 cases. Koch<sup>22</sup> has also reviewed the literature dealing with *in vivo* measurements of the size of the retinal arterioles, and has reported a large series of additional measurements.

The most striking feature of the normal histology of the retinal arterioles is the fact that the media consists mainly of collagenous tissue with a very small admixture of smooth muscle. Therefore it is impossible to differentiate sharply between subendothelial proliferation, medial hypertrophy, and perivascular fibrosis. The measurements reported by Manlove<sup>28</sup> show that the characteristic change in the retinal arterioles of hypertensive patients is a considerable decrease in the diameter of the lumen and a corresponding increase in the thickness of the wall. The ophthalmoscopic measurements of Koch<sup>22</sup> show that there is a progressive reduction in the caliber of the retinal arterioles as the severity of the hypertensive state increases, but the frequency of occurrence of reversible spasm in the retinal vessels is still a controversial point. Manlove's measurements on the choroidal arterioles show that the changes in the L/W ratio are of the same order as those observed in the retina, but all authors who have compared the degree of arteriolosclerosis in the retinal and choroidal vessels agree that the changes tend to be more severe in the choroid.

**Summary.** In this review, emphasis has been placed on those investigations in which an attempt has been made to obtain quantitative data on the state of the arterioles in various organs and tissues of hypertensive patients. A review of the published results of such investigations shows that the data, though seriously incomplete in many important respects, are sufficient to justify the following provisional hypotheses concerning the relation between hypertension and arteriolosclerosis:

1. Arteriolosclerosis is a primary "aging" process, analogous to arteriosclerosis of the large arteries, but modified in its histologic characteristics by differences in the normal structural properties of the walls of vessels of different sizes.

2. In the absence of hypertension, the incidence of arteriolosclerosis increases

gradually with age, although the incidence and severity of the process vary widely in different parts of the body. For example, arteriosclerosis is extremely common in the spleen, but relatively infrequent in other organs such as the kidney.

3. In hypertensive patients, there is a marked increase in the incidence and severity of arteriosclerosis, not only in the kidney, but also in almost all organs and tissues which have been studied by quantitative methods. However, all observers agree that arteriosclerosis is completely absent from the kidneys of a small but definite percentage of patients with undoubted essential hypertension. Moreover, although the evidence cannot be regarded as conclusive, the majority opinion in the literature at the present time does not support the hypothesis that renal ischemia of sufficient degree to initiate the Goldblatt pressor mechanism can be produced by the relatively mild degrees of arteriosclerosis which are observed in the kidneys of a large per-

centage of hypertensive patients, especially in the early stages of the disease.

4. The most satisfactory explanation of the available evidence would seem to be that arteriosclerosis (an organic "aging" process) and essential hypertension (a "functional" hemodynamic disturbance of unknown etiology) are both primary independent processes which may undergo parallel development, but which are capable of intensifying one another in the later stages of their evolution.

The disappointingly inconclusive nature of these hypotheses, and the inadequacies of the data on which they are based, should call attention to the serious deficiencies which still exist in the information now available on the state of the arterioles in essential hypertension. It is hoped that this review may serve to emphasize the need, not only for further studies by ordinary histologic methods, but also for the application of new techniques which will give a clearer picture of the hemodynamic characteristics of the arteriolar bed in hypertensive patients.

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## PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

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## EPIDEMIOLOGIC IMPLICATIONS OF DEVELOPMENTAL ARRESTS

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THE many years that Stockard gave to the clinical and experimental study of monstrosities and abnormal forms of life led him to regard them collectively as a disease entity.<sup>31a</sup> He believed them susceptible of analysis in respect to cause and effect; and to conform to basic biologic laws. He did much to lift developmental arrests of man from the realm of medical curiosities and peculiar unexplained aberrations of nature. Furthermore, he introduced the concept in 1909 that here was a problem of the public health—a mass phenomenon of disease “which causes the death of about 23 % of the human race before or shortly after the time of birth and handicaps a certain proportion of the survivors throughout their lives.”<sup>31b</sup>

That developmental arrests are something more than a collection of isolated events affecting scattered individuals, that collectively they constitute a problem of grouped populations and have community health significance has been an attitude of slow evolution. Yet the pattern of this developing appreciation is not unlike that which has characterized most epidemiologic problems in public health, from the communicable diseases through cancer and diabetes to automobile accidents.

The initial interest in congenital anom-

alies was clinical. It led to a great collection of case reports as far back as the 17th century, naturally concerned with bizarre and unusual rather than minor malformations of more frequent occurrence. The next development was evident almost 200 years ago in an attempt at classification by purely morphologic criteria. Etiologic interpretation, surprisingly far advanced in 1832 by Geoffroy Saint-Hilaire,<sup>28</sup> was given great impetus by numerous experimental<sup>11,21,23,30</sup> and embryologic<sup>22a,b</sup> studies at the beginning of this century. New momentum was added by epidemiologic observations of the past decade,<sup>16a,b</sup> which confirm the existence of a public health problem. A concept of its nature begins to take form. Its extent in detail and design remains ill defined.

What has thus far been brought out is perhaps best introduced by a brief consideration of the clinical nature of some of the congenital anomalies. If those of the head alone are even cursorily surveyed, no organ, tissue, or feature will be found to escape occasional anomalous development or even complete ablation. The most bizarre form is ablation of the whole head, or acephaly, which is not incompatible with brief postnatal life. By comparison, anencephaly approaches the natural—with the supernatural dicephalic

monster at the oposite extreme. Besides Janus there is Cyclops and a host of grotesque variations from the Greek faun of antiquity with his primitive ear to the "mongolian idiot," incorrectly so designated in 1866 by Langdon Down because of the slant eyes and brachycephalic head. The list of cephalic anomalies is merely begun. Microphthalmia, malformed ears, cleft palate, hare lip are common enough, but the names give no indication of the groupings of associated deformities or the transitional forms between such classes.<sup>35</sup> Is a mongoloid child with a cleft palate not just as logically an instance of cleft palate with associated mongolism? Is a boy with such a minor anomaly as a cleft uvula a normal individual or a patient with minimal cleavage of the palate?

Such questions illustrate the difficulty of classifying developmental arrests morphologically. Practically, the problem has been met, though not solved, by the common selection of the most dramatic clinical deformity of an associated group in naming the condition. Thus, the single eye is the primary stigma which identifies cyclopia, while the constantly associated proboscis-like deformity of the nose is ignored. It is reasonable to believe that no one deformity is of greater biologic significance than another. Each is part of a broader pattern. Such patterns may well be significant in interpreting the peculiarities and reactions of host and agent which lead to their production.

Clinical causes of developmental arrests have remained obscure, with perhaps one outstanding exception. The rôle of syphilis has long been appreciated. The likelihood of the syphilitic mother to produce, after several abortions and a macerated fetus, a child showing Hutchinsonian stigmata followed by a normal child, is classical teaching. No attempt is made to discount the importance of hereditary factors in the general problem of congenital anomalies, but at least they are not implicated in those developmental arrests of syphilitic origin, and probably not in most others.

The morphologic characteristics of

anomalous conditions provide a basis for their embryologic interpretation.<sup>22a,b</sup> Even when the cause of the associated arrests cannot be determined, the time of their origin and the sequence of events thereafter can often be delineated with reasonable accuracy.

Epidemiology has thus far scarcely been concerned with this field. That a baby born with no head might have suffered from the same disorder as a baby born with two heads has seemed too absurd to warrant evaluation. The first is called acephaly, the second dicephaly, with the implication that they represent as many unknown diseases as there are names. When multiple deformities co-exist, one is ordinarily accorded primary emphasis and the others become secondary. When the deformity is severe, the child is a monster; when less severe, it is a developmental arrest; and when minimal it is regarded as inconsequential and of no significance.

Epidemiologic events of the past decade now make evident that the principles discovered a generation ago to underlie abnormal forms of lower animal life, in all likelihood apply equally to human arrests. These principles based upon studies accumulated through 200 years were clarified and formulated by Stockard<sup>31c</sup> as follows:

1. Every type of developmental monster known in the literature may be produced by one and the same experimental treatment.

2. The same structural abnormality may be induced in the embryos of various species by a great number of different experimental treatments.

3. The type of monster or deformity is determined by the developmental period in which the arrest is induced.

It cannot be said, to be sure, that "every type of developmental monster" in man has been observed to follow rubella, but certainly congenital cataract, heart disease, dental defects, microcephaly and mental retardation have been demonstrated as its occasional sequelæ.<sup>34</sup>

Early in 1941 Gregg, an ophthalmologist,<sup>16a,b</sup> noted among babies in Australia a relatively large number with congenital cataract. In 68 of the 78 collected cases the child's mother was found to have contracted rubella while pregnant. Prior to 1939-1940 no appreciable epidemic of this disease had existed in Australia for 17 years. The opportunity had arisen for the accumulation of a large number of susceptible young adults, including women in the child-bearing age.<sup>3</sup> Of seeming significance was the fact that so far as could be ascertained the rash had appeared with great regularity in the early months of pregnancy. Gregg hypothesized a causal relationship between rubella and the observed congenital defects.

In order to determine the significance of Gregg's observations a commission was established,<sup>32a,b</sup> headed by Swann, to confirm the diagnosis and investigate the subsequent history of patients contracting an exanthematous disease during pregnancy. The commission confirmed Gregg's observation that maternal rubella was associated with subsequent developmental arrests of the lens and the heart. Maternal infection had occurred in 29 of 31 such instances during the first trimester of pregnancy. The series has been extended by other investigators.<sup>1,9,12,17,20a,25,27</sup> Of 136 such cases analyzed by Conte *et al*,<sup>10</sup> 72% had cataract, unilateral or bilateral; 61% had mental retardation; and 58% congenital heart disease. At least 53% had multiple anomalies. The grouping of rubella by month of gestation is shown for 100 babies with developmental arrests. (Fig. 1.)

The significant aggregation of cases in the first trimester confirms Gregg's original hypothesis of a causal relation between maternally contracted rubella and developmental arrests. The data indicate that congenital cataracts and congenital heart

disease, mental retardation, and dental defects<sup>13</sup> characterizing these babies originated as a rule in the first trimester of pregnancy. The epidemiologic data are entirely consistent with the embryologic fact that the lens\* and heart† undergo definitive differentiation during that trimester of pregnancy.

The actual risk of deformity to the fetus as a result of rubella in pregnancy is not indicated by the figures cited in the Australian studies. That the fetus may escape clinically evident arrests was shown by Swann and his co-workers<sup>32a,b</sup> and by Fox and Bortin;<sup>14</sup> that the fetus may die was suggested by evidence presented by Aycock and Ingalls.<sup>3</sup> The available epidemiologic data were consolidated and extended by Ober, Horton and Feemster.<sup>24</sup>

Of 40 pregnancies complicated by maternal rubella in the first trimester, 80% resulted in abortions or still births, 32% in babies with congenital arrests, while 50% were apparently normal. Of 36 instances of rubella in the second and third trimesters, 8% resulted in abortions or still births, 6% in babies with developmental arrests, and 86% in apparently normal infants. Minor arrests and minor degrees of mental retardation cannot be excluded without exhaustive studies and longer observation.

These facts furnish definite epidemiologic evidence that an environmental agent operating after fertilization of the human ovum may kill the embryonic host or merely arrest the development of particular organs. The principle has long been accepted as regards syphilis, but its extension and application to such a simple disorder as rubella implies that other simple disorders are likewise effective agents in the production of arrests.

Rubella is now revealed as an agent capable of acting during many weeks of early pregnancy to produce a variety of

\* Lens fibers are evident shortly after a month of gestation and "toward the end of the third month the primary lens fibers attain a length of 18 mm., whereupon they cease forming new fibers by cell division."<sup>2</sup>

† "The critical period for the development of congenital cardiac defects is from the fifth to the eighth week of intrauterine life, during which the septa are forming, the bulbus cordis is undergoing involution, and torsion of the great vessels is taking place."<sup>4</sup>

arrests. By contrast, mongolism has recently been demonstrated by embryologic methods to be a syndrome of multiple arrests originating at about the eighth week of fetal life.<sup>18a</sup> By epidemiologic methods, an association has been developed between mongolism and maternal uterine or systemic disease of varying nature, present or operating at about the stated time.<sup>18b,19</sup>

were about 40 years, and most of the other group about 24 years old (Fig. 2). An association between mongolism and relatively advanced age of the mother is clearly evident, a circumstance of itself giving proof of a maternal factor operating in causation. The several irregularities in distribution at younger ages indicate that additional factors other than advanced age must operate.

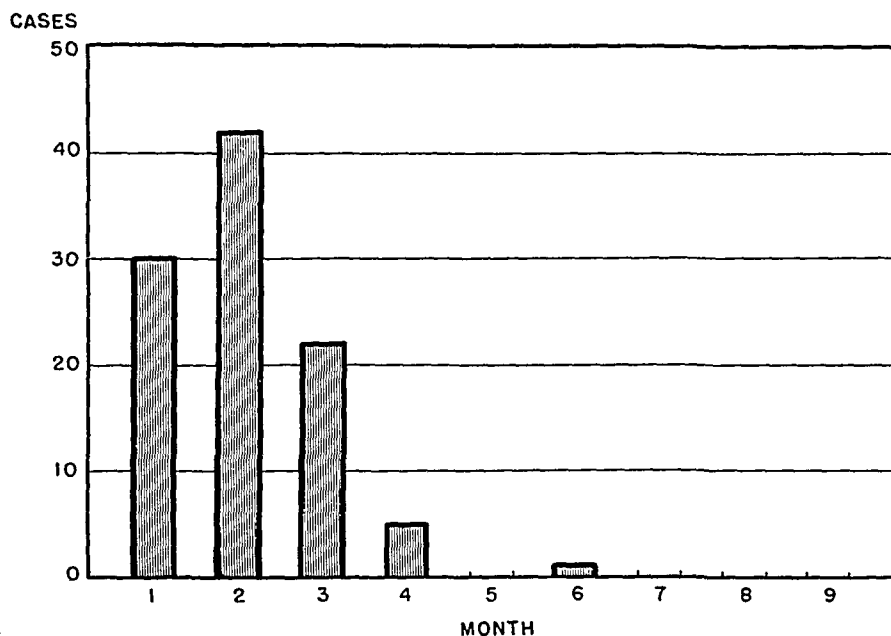


FIG. 1.—Congenital defects (of the lens, heart, teeth, skull and brain) following maternal rubella, by month of pregnancy.<sup>3</sup>

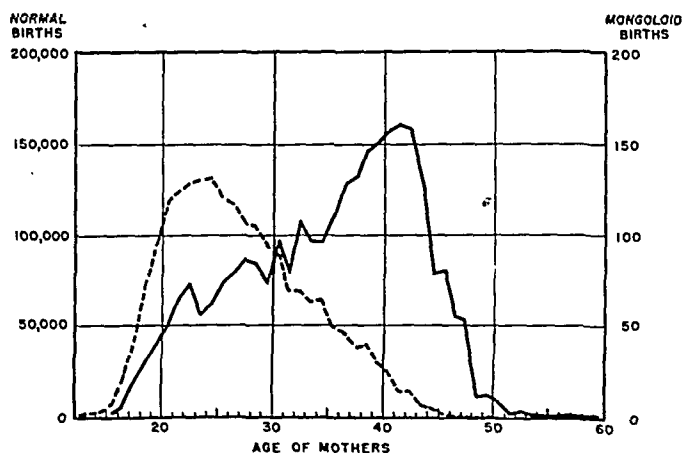


FIG. 2.—Age distribution of mothers of normal babies, United States 1934 (broken line) and of mothers (2822) of mongoloid babies (heavy line).<sup>8</sup>

Bleyer<sup>8</sup> plotted the ages of 2,822 mothers who gave birth to mongoloid infants against the ages of more than 2,000,000 mothers in the United States who produced normal infants during 1934. Most of the mothers producing mongoloid offspring

Three factors have been identified in the causation of mongolism—gestational hemorrhage, mechanical disorders of the uterus, and intercurrent infection. Gestational hemorrhage was associated with mongolism in 20.4% of 216 mothers studied

by Schroeder,<sup>29</sup> Beidleman<sup>5</sup> and Benda.<sup>6</sup> The incidence of gestational hemorrhage was less than 1 % in a series of 248 mothers producing normal babies.<sup>29</sup> The time of the hemorrhage (Fig. 3) tended to center at the end of the second month of gestation.<sup>18b</sup>

In 9 of the 11 reported instances of intercurrent infection complicating pregnancies productive of mongoloid children, the infections centered in the second and third months (Fig. 4). Three of the 9 were rubella;<sup>7,10,19</sup> the others included influenza 3,<sup>15,19</sup> purulent otitis media 2 and

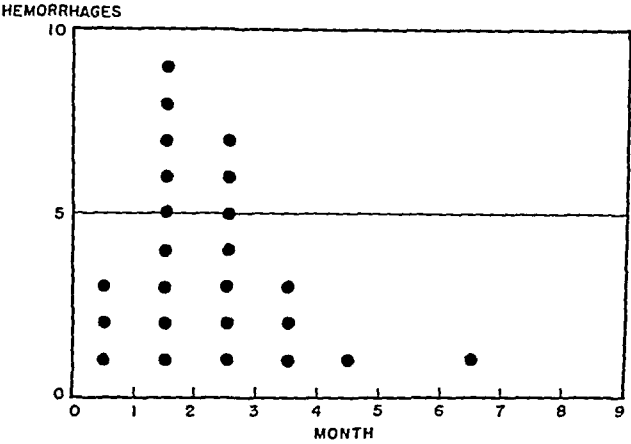


FIG. 3.—Distribution of maternal hemorrhages (24) by month of pregnancy of mothers (16) of mongoloid babies.<sup>5 6</sup>

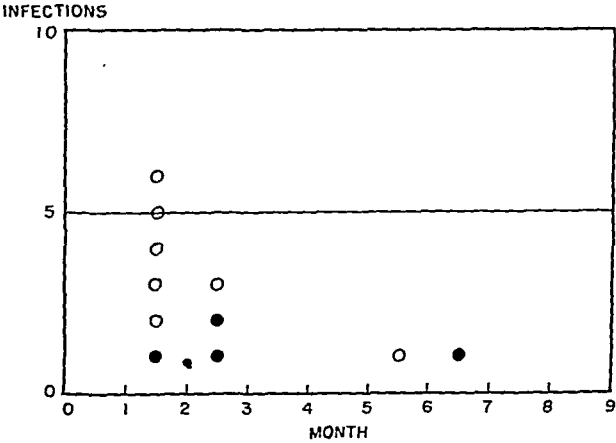


FIG. 4.—Maternal infection and mongolism. Distribution of rubella (black dot) and other infections (white dot) by month of pregnancy.<sup>7 10,15,19</sup>

By gynecologic examinations Schroeder found 26 % of 99 mothers of mongoloid babies to have a significant degree of retroflexion or prolapse of the uterus, while only 5.5 % of 248 mothers of normal babies had such abnormalities. Pathologic changes, including myomata of the uterus, were encountered more frequently in the older age group of the mongoloid series and corresponded in general with gestational bleeding.

mumps. The number of cases is small but their occurrence at the period known to be significant for the production of mongolism is suggestive.

Similar epidemiologic methods applied to encephalo-ophthalmic dysplasia (Retro-lental Fibroplasia) have confirmed Terry's observation of an association with prematurity and multiple pregnancy.<sup>33</sup> Half of 26 patients whose birth weights are recorded, weighed under 3 pounds at

birth; two-thirds of a series of 77 infants weighed less than 5 pounds.<sup>20,26b</sup> Furthermore, it was found that 11 (14%) of 77 mothers had multiple births; 8 (10%) had intercurrent infections; 3 (4%) had toxemia of pregnancy; 2 (3%) had placenta previa; and 18 (26%) gestational hemorrhage. The relation of anomalies to the maternal condition was indicated by the frequency of toxemia of pregnancy, multiple births, and placenta previa as compared with chance expectancy, and by the grouping of hemorrhages and intercurrent infections during or shortly after the second trimester of pregnancy.<sup>18c</sup>

logic criteria. At present, the positions of the post-rubella defects, mongolism and encephalo-ophthalmic dysplasia are the only prenatal patterns which have been confirmed by epidemiologic and embryologic evidence. The other examples of arrests acquire their position on embryologic evidence only. Evidence is not sufficiently refined for even the best observed agents, syphilis and rubella, to plot their precise temporal relationships to specific sequelæ. Indeed, for a chronic disease like syphilis, of necessity the period of activity must be inferred from the nature of the arrests rather than measurable clinical manifesta-

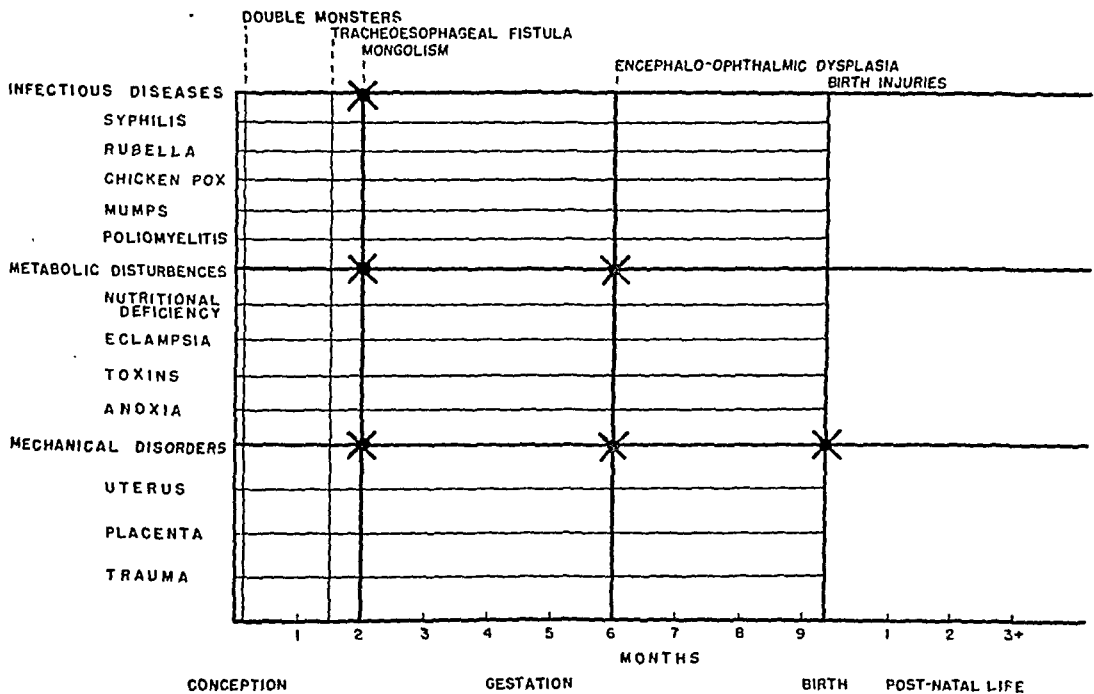


FIG. 5.—Schematic presentation of the origin of developmental arrests.

The general implication of these several phenomena is that they are the clinical expression in man of the principles demonstrated to operate in lower animals. This relation can be illustrated by arranging established patterns of grouped arrests as ordinates along a base line representing periods of fetal development (Fig. 5).

If agents proven or suspected of producing arrests are plotted as abscissæ, a grid results on which certain points represent associated cause and effect judged by epidemiologic as well as embryo-

logic criteria. Further refinement of knowledge can be expected to come by relating the acute rather than the chronic illnesses of pregnancy to their arrests. Since a considerable clinical error is often present in respect to actual date of conception, this method of approach presents obstacles.

The specific implications to be derived from these collected observations on rubella, mongolism and encephalo-ophthalmic dysplasia are first, that epidemiologic methods of study may profitably be applied to investigation of many chronic diseases of the child originating in the

developmental period of life, where the origin is not clearly due to hereditary factors. These conditions would presumably include a considerable segment of the diseases of human beings. Some become apparent only after many years.

Secondly, if mechanical disorders of the uterus, placental hemorrhage and intercurrent infections are causative factors in respect to certain recognized arrests at particular periods of gestation, then it is reasonable to assume that they may operate at other periods. That rubella has thus far been identified only with arrests of the first trimester may prove to be more apparent than real. Consequences of an entirely different nature and conspicuousness would be expected to follow the disease in the second and third trimesters. For example, the demonstration of spina bifida in possible relation to such an illness would take an entirely different technic (radiologic) to prove or disprove, as compared with congenital cataract (ophthalmologic).

**Summary and Conclusions.**—The period of prenatal development is of crucial significance in shaping the individual's

ultimate physical status. Disease of the mother reacting on the fetus may result in death, disability, or recovery without residual effect (*i. e.*, escape) on the infant. Maternal intercurrent infection, metabolic diseases and mechanical disorders of the uterus are the principal agents. Rubella to date is the best example with its arrests demonstrably related to development during the first trimester of pregnancy. Those of mongolism occur about the eighth week and those of *encephalo-ophthalmic dysplasia* during or shortly after the second trimester. Others await definitive evaluation.

Three principal epidemiologic implications become evident in respect to developmental arrests. Unrelated agents acting during pregnancy may give rise to the same type of arrest. Different types of arrest may be caused by a single agent. The resulting anomaly is expectedly a function of the stage of development at which the agent is active. Patency of the cardiac septum cannot come into being as a developmental arrest after the septum has closed; nor an imperforate anus after the anal membrane has perforated.

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## LEPROSY IN VETERANS OF AMERICAN WARS

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Most of the communicable diseases now implanted in the American population were imported to this continent as part of the general global spread of infectious processes that gained prominence in the 15th and 16th centuries, and still continues. This broader dissemination of infectious agents came about chiefly through expanding trade and travel.<sup>9</sup> The amount and rapidity of international transportation of men and animals continue to be governing factors that determine the gradual transition that is taking place from a state of isolated foci of particular diseases scattered throughout the world, but periodically disturbed by pandemic spread of some one or other; to that of a world which is now becoming one epidemiological unit.<sup>33</sup>

The history of epidemic disease in the United States would indicate that the majority of our domestically common infections were imported—measles, diphtheria, smallpox and undulant fever, to name a few. Some appear definitely to be indigenous diseases of pre-Columbian America, such as tularemia, Rocky Mountain spotted fever, coccidioidomycosis and Chagas' disease of South America. The status of others is less precise, with conflicting evidence as to whether they are native to North America or imported within historical times. The well known controversy about syphilis is in point. At any rate, the number derived from these several sources is imposing, as indicated by the list of official reportable conditions to health departments. Many others are recognized through epidemiological<sup>34</sup> and clinical<sup>22</sup> descriptions. Leprosy of North America is very definitely an imported disease.<sup>15b, 19</sup>

Unlike measles, smallpox, and so many other imported diseases, leprosy has never become generally implanted in the American population. The currently existing major foci of infection include the Southern States of Louisiana, Texas and Florida;<sup>3</sup> but even here the number of cases has never been great. Minor foci have existed in California and South Carolina.<sup>17</sup> Georgia, Alabama and Mississippi<sup>15d</sup> contribute occasional cases among native born Americans and scattered representation comes from some half dozen other states. Minnesota and neighboring states comprised a focus of leprosy for a number of years.<sup>5</sup>

Prolonged and intimate exposure as a requirement for the transmission of leprosy has been widely used to explain the striking tendency toward localized and familial occurrence, a well known characteristic of the disease.<sup>30</sup> Whether the idea of long exposure is based on actual evidence or is merely an assumption evolved to fit the observed distribution into the contagionist point of view, is open to question. The concept of "prolonged and intimate exposure" and the variability in the incubation period are both sufficiently broad to permit explanation of the distribution of cases under almost any circumstances of time and space; notably the restricted occurrence, and failure to follow usual laws of contagion. On the other hand, a number of epidemiologic features of the disease are inconsistent with such a view.

In the first place, many studies of "leprosy in relatives" show a concentration of cases in distant relatives ordinarily not living under conditions of "prolonged and intimate exposure." Perhaps the most striking example is the long con-



tinued occurrence of the disease in the two widely separated foci on the North American continent, in the same racial stock and in individuals known to be related.<sup>2a</sup> It is further significant that the disease did not exist in either population until many years after they were separated in 1755. In communicable diseases as a group such as measles, German measles, diphtheria, and scarlet fever, secondary attack rates in families beyond childhood age are uniformly higher in females. This seems clearly due to the fact that the adult female is subject to more "prolonged and intimate exposure" within the family than the adult male. Under similar conditions of exposure and measured in terms of person years, secondary familial attack rates in leprosy preponderate in males by about 2 to 1.<sup>12b</sup> The only explanation offered, even by the contagionist school of thought, is a different inherent susceptibility in the two sexes.<sup>12a</sup>

The extraordinary infrequency of conjugal leprosy as compared with its occurrence in blood relatives, within the household and more distant, is one of the strongest arguments against prolonged and intimate exposure as an essential factor in transmission. The common explanation is that the individuals concerned are past the susceptible age—a supposition not borne out by the age distribution of leprosy, nor by data here presented in respect to persons first exposed in adult life (Spanish-American War veterans). Using a modified life-table method, Doull *et al.*,<sup>12b</sup> brought out that secondary attack rates for lepromatous cases decreased, as age at first exposure increased. It is not clear, however, to what extent these results may have been affected by removal of susceptible individuals from older age groups through having already developed the disease as primary cases.

Previous studies of regional, racial, and familial selectivity in the occurrence of leprosy on the North American continent<sup>2a,2b,4</sup> are in keeping with the view expressed by Sir James Simpson in 1842<sup>32</sup>

and now generally accepted, that the major determinant is neither hereditary transmission nor prolonged and intimate exposure, but probably ordinary exposure in regions, in racial stocks, and in families with an hereditary susceptibility to the infection.

In 1882 Hirsch<sup>19</sup> wrote "the best ground on which to try this question is obviously afforded by the small closely circumscribed and therefore easily surveyed leprosy-spots, with a fixed population subject to no changes where the state of health in the several families may be learned with the least possible trouble and followed with certainty through a long series of generations."

The incidence of the disease in native-born Americans serving in the Armed Forces, and in veterans of our wars, affords an opportunity for observations<sup>31</sup> on the incubation period of the disease, on prolonged intimate exposure as a requirement for production of the disease, and on inherited susceptibility as a major determinant in the tendency to familial occurrence. The study is particularly worthwhile in that the respective theaters of war presented variable opportunities for exposure to leprosy,<sup>35</sup> and because of the varied regional, racial, and familial origin of patients among the members of the Armed Forces. The first requisite in evaluating the relative significance of host susceptibility and continued exposure is to note the relative frequency of leprosy in the several theaters of war in which our armies operated, and to determine the origin by place of birth of those who contract the disease during service or thereafter. The time relationships to place and length of service are likewise necessary.

The best historical accounts indicate that leprosy was first introduced to the American continent in the middle of the 18th century. White<sup>38</sup> states that it was present in Louisiana in 1758 and good evidence exists that Florida was involved about 1775;<sup>15d</sup> in both instances presumably through the slave trade and the West Indies. No known information suggests

the presence of the disease at the time of the Revolutionary War in the northern colonies or in other areas where that war was fought.<sup>18b</sup> Troops of the American Forces may be assumed not to have been at risk. At any rate, study of a variety of sources<sup>6,25</sup> fails to give record\* of the occurrence of leprosy among soldiers of this war period or in veterans thereafter.<sup>1</sup>

The war of 1812 did involve the element of risk since leprosy is known to have existed for some 70 years in New Orleans, the principal theater of war. Again no record of military cases can be found.<sup>10,21</sup> Leprosy in the general population was certainly not common and the number of troops, judged by standards of subsequent wars, was not great. The medical records of the Army<sup>23</sup> of that day were, however, not such that assurance can be had of the absence of the disease.

The complete lack of reports of leprosy in connection with the Mexican War of 1846 or among veterans of that war is more difficult to understand. The war lasted two years. The number of men involved was appreciable and Mexico had long had leprosy in considerable numbers. Hirsch<sup>19</sup> states that it occurred "in general diffusion, mostly indeed among native Indians, both on the coast and in more elevated, if not even the highest points." He cites medical reports of its existence at least in 1838. Army records are available in greater detail and number, and yet mention of leprosy is absent,<sup>13a,b,27a,b,c,d,e,28,29</sup> both in the period of the war and in the years that followed.<sup>8</sup> The experience of later American wars fought in similar foci of infection discounts the validity of conclusions which might be drawn from this negative evidence. Epidemiological considerations would suggest that the disease may well have occurred in veterans of this campaign. Indeed many years passed after the Spanish-American War of 1898 before the association of temporary station in a foreign endemic focus and the later

development of the disease among veterans was established.

The Civil War was fought in domestic territory in regions essentially free of leprosy. The lack of reported cases<sup>16,24</sup> is in agreement with what must have been a minimal risk. Reliable information on leprosy as a feature of military operation in the fields is available for the last 3 wars of our history.

**TIME RELATIONSHIPS.** From 1921 to 1940, 32 Spanish-American War veterans were admitted to the U. S. Marine Hospital at Carville, La., suffering from leprosy. Thirty patients had military service outside the United States in places known as foci of leprosy: Puerto Rico, Cuba, Hawaii, China—25 in the Philippines. Two had not; one coming from Louisiana and the other from Texas, both states being recognized foci of the disease. Five of the group were born outside the United States. Of those born in the United States, 19 were from parts of the country that are not foci of the disease.

During the same period, 51 World War I veterans were admitted to the National Leprosarium. The records of 33 show no service outside the United States and only 6 had a record of service in foreign countries which are foci of the disease—1 in the Philippines. Eighteen were born outside the United States, 33 in the Southern tier of states and none north of this region.<sup>18a</sup>

As of 1946, 28 cases of leprosy have occurred in veterans of World War II.<sup>11</sup> Thirteen men were born in foreign countries, and 11 in the United States, of whom 10 were from states known to be foci of the disease. Only 1 was born outside such areas.

Cases occurring during these wars are listed in Tables 1, 2, and 3, showing age at first symptoms as nearly as could be ascertained, place of birth, place from which admitted to the leprosarium, descent, and date of onset of the disease.

\* The information on leprosy in relation to the earlier wars of the United States is furnished by Colonel J. H. McNinch, Director of the Army Medical Library, War Department, who conducted a careful search of military records and published reports not ordinarily available.

The veterans of the Spanish-American War had their origin, both by birth and by place of admission, in widely separated localities. Veterans of World War I, both native-born and foreign-born, by birth and place of admission, originated largely in areas known to be foci of the disease. Veterans of World War II (place of admission not shown since admissions have been directly from the military service)

following military service. The first case, born in Iowa and admitted from Nebraska with no history of other exposure, is presumed to have been exposed in the Philippines during military service from 1898 to 1899 and therefore to have developed the disease after an unusually short incubation period. The last case developed the disease in 1938; was born in Missouri, and admitted from Missouri;

TABLE 1.—LEPROSY. SPANISH-AMERICAN WAR VETERANS

Native-born					
Record No.*	Age 1st symp.	Place of birth	Place of adm.	Descent	Date 1st symp.
16 (306L)	32	N. C.	D. C.	Scotch-Ir.	Ab. 1905
80 (335L)	45	Mich.	Mich.	Not given	Not given
93 (93)	47	Penna.	Fla.	" "	Ab. 1915
144 (144)	37	Missouri	Kan.	" "	Ab. 1915
176 (176)	56	Penna.	Philippines	" "	Not given
186 (186)	51	La.	New Orleans, La.	" "	1921
230 (230)	40	La.	New Orleans, La.	" "	Ab. 1913
244 (244)	32	Texas	Texas	" "	1907
250 (250)	33	Ala.	Ga.	" "	1916
312	57	N. C.	Va.	" "	1924
351	50	Ohio	Ohio	German	1924
389 (389)	39	Iowa	Ill.	Not given	1924
433	45	R.-I.	Kan.	French	1923
450	40	Ark.	N. Y.	Eng.-Irish	1923
484 (484)	41	Ky.	Mont.	Not given	1906
571 (571)	48	La.	New Orleans, La.	" "	1923
626 (626)	51	Texas	Texas	" "	1923
641 (641)	45	Ind.	D. C.	" "	1919
774	42	Ga.	Ga.	American	Ab. 1921
907	36	Iowa	Neb.	German	Ab. 1901
951 (951)	42	Ohio	Calif.	Not given	Ab. 1916
1009 (1009)	50	Penna.	Philippines	Dutch	1930
1009 A	59	Ohio	Philippines	German	Not given
1242 (1242)	53	La.	New Orleans, La.	Not given	Ab. 1935
1290	66	Va.	Ohio	Am.-Negro	Ab. 1935
1330	59	Mich.	Texas	Irish-Am.	Ab. 1934
1376	55	Missouri	Missouri	Not given	1938
Foreign-born					
280	44	Germany	Wisconsin	German	Not given
292	49	Bohemia	Va.	Bohemian	1921
364	41	Ireland	Hawaii	Irish	1916
1057	37	Russia	N. Y.	Jewish	1922
1286	58 (25?)	Germany	Ga.	German	1933 (1900?)

\* National Leprosarium.

by place of birth, largely originate in areas known to be foci of the disease.<sup>7</sup> More than half of the foreign-born originated in the Philippine Islands.

Chart I shows native-born veterans of the three wars according to the time they developed the disease, and according to whether they were born in recognized foci of the disease or in other areas of this country. Cases in Spanish-American War veterans developed in from 3 to 32 years

and was in the Army in the Philippines from 1906 to 1908 (included with Spanish-American War veterans). Since there is no history or presumption of other exposure, this patient would appear to have developed recognized symptoms of the disease 30 years after exposure. It should be stated, however, that a number of veterans who developed the disease following the Spanish-American War cannot be assumed to have had incubation periods

as long as indicated, because of residence in the Philippines, either as members of the Army or as civilians, for many years following the Spanish-American War itself.

Of 18 cases in Spanish-American War veterans<sup>26</sup> (on whom data are available),

who came from places which are not domestic foci of the disease, the periods during which exposure in foreign foci could have occurred range from 9 months to 32 years, as shown in Table 4. Perhaps it should be emphasized that these figures

TABLE 2.—LEPROSY. WORLD WAR I VETERANS

<i>Native-born</i>					
Record No.*	Age 1st symp.	Place of birth	Place of adm.	Descent	Date 1st symp.
52 (314L?)	24	La.	La.	Not given	1919
95	22	La.	Calif.	" "	1919
113	32	La.	La.	" "	1919
123	43	La.	La.	" "	Not given
145	23	Fla.	Ill. (Fla.?)	Am.-Negro	1918
197	24	Fla.	Fla.	" "	1919
215	28	Texas	Calif. (Texas?)	American	1921
228	24	Fla.	Fla.	Eng.-Scotch	1919
231	18	Texas	Texas	English	1917
246	30	New Orleans, La.	Mississippi	Am.-Negro	1918
272	27	Texas	Texas	" "	1919
300	26	La.	New Orleans, La.	Not given	1917 (1921)
337	20	La.	La.	" "	Not given
390	26	La.	New Orleans, La.	" "	1919
414	22	Mississippi	Mississippi	Negro	1919
489	31	Ga.	Tenn.	Am.-Negro	Ab. 1919
562	31	La.	New Orleans, La.	" "	1921
608	27	Texas	Texas	Not given	1919
659	33	New Orleans, La.	New Orleans, La.	Am.-Negro	1929
689	24	New Orleans, La.	Va.	German-Ir.	1918
723	23	Texas	Ind. (Chicago?)	American	Ab. 1919
736	35	La.	Okla.	French	1927
746	18	Texas	N. Y.	Jewish	Ab. 1919
816	24	Texas	Texas	Mexican	1919
827	27	La.	La.	French	Ab. 1923
833	31	Texas	Texas	Irish	Ab. 1920
850	31	La.	La.	Am.-Negro	1929
931	34	Mississippi	La.	" "	1932
965	19	Fla.	Fla.	American	1919
999	41	New Orleans, La.	New Orleans, La.	Irish	1933
1114	38	Texas	Texas	Mexican	Ab. 1934
1172	35	Fla.	Fla.	Irish	Ab. 1930
1319	41	Texas	Texas	"	1937
1041	20	Mississippi	Ark. (Okla.?)	Ir.-Dutch	Ab. 1919
1314	27	La.	Texas	French	Ab. 1930
<i>Foreign-born</i>					
100	24	Philippines	Mass.	Filipino	1918
102	24	India	Mass.	"	Not given
139	26	Br. Guiana	Ill.	English	1917
192	22	Puerto Rico	N. Y.	Puerto-Rican	Not given
198	25	Br. W. Indies	N. Y.	English	1920
225	22	W. Indies	Va.	Not given	1919
294	26	Bahamas	Neb.	English	1922
301	27	Philippines	Maryland	Filipino	1923
311	22	Virgin Islands	Va.	Negro	1923
401	26	Greece	N. Y.	Greek	Ab. 1917
579	33	Italy	N. Y.	Italian	1922
727	27	Br. W. Indies	N. Y.	Port.-Eng.	Ab. 1919
732	44	Philippines	Calif.	Filipino	Ab. 1929
733	28	Philippines	Calif.	"	1925
741	37	Philippines	Calif.	"	Ab. 1928
893	39	Philippines	Wash.	"	1932
899	24	Greece	Calif.	Greek	1918
1320	39	Philippines	N. Y.	Filipino	1938

\* National Leprosarium.

represent the periods during which they were in countries, particularly the Philippines, which are known as foci of the disease. No data are available on length or intimacy of exposure, but military life by its very nature is not conducive to living conditions ordinarily interpreted as those of the "prolonged and intimate exposure" associated with leprosy.

served in foreign foci. It thus would appear that a small outbreak of leprosy occurred in native-born Americans which can be attributed to exposure to the disease in foreign foci in the course of service in the Spanish-American War. The usual limited numbers arising from exposure in domestic areas are in addition.

Of the veterans of World War I who

TABLE 3.—LEPROSY. WORLD WAR II VETERANS

<i>Native-born</i>				
Case No.	Age 1st symp.	Place of birth	Descent	Date 1st symp.
1	..	New Orleans, La.	American	1942
2	..	Calif.	Japanese	1941
3	22	Texas	Mexican	1941
4	16	Calif.	American	1937
5	33	New Orleans, La.	"	1941
6	24	Illinois	Jewish	1943
7	23	Calif.	Japanese	1943
8	..	Texas	Mexican	1944
9	25	La.	American	1944
10	26	Texas	Mexican	Ab. 1944
11	30	Texas	American	1941
<i>Foreign-born</i>				
12	..	Mexico	Mexican	Not given
13	..	Philippines	Filipino	Ab. 1938
14	26	"	"	Ab. 1929
15	..	"	"	Ab. 1941
16	36	Mexico	Mexican	Not given
17	39	Philippines	Filipino	" "
18	..	Puerto Rico	Puerto-Rican	" "
19	31	Philippines	Filipino	" "
20	18	Honolulu	Hawaiian-Chinese	Ab. 1943
21	27	Br. Guiana	..	Not given

TABLE 4.—LEPROSY. SPANISH-AMERICAN WAR VETERANS—PERIODS OF PROBABLE EXPOSURE

Case No.	Place of birth	Duration of stay in focus	Case No.	Place of birth	Duration of stay in focus
280	Germany	9 mo.	1057	Russia	3 yrs.
907	Iowa	1 yr.	16 (306L)	N. C.	5 "
389	Iowa	2 yrs.	433	R. I.	12 "
484	Ky.	2 "	176	Penna.	16 "
1330	Mich.	2 "	292	Bohemia	17 "
1376	Mo.	2 "	364	Ireland	18 "
250	Ala.	2½ "	961	Ohio	18 "
774	Ga.	2½ "	1290	Va.	25 "
641	Indiana	3 "	1009	Penna.	32 "

Of the Spanish-American War veterans who were born in foci of the disease in this country, the first 2 developed the disease in 1907 and 1913 respectively, had no record of foreign service, and therefore may be assumed to have contracted the infection as the result of exposure where they lived. The other 4 patients came from domestic foci of the disease and also

have developed leprosy, all were born in foci of the disease in this country, and in contrast with those of the Spanish-American War, either developed the disease within a relatively few years of World War I, or already had the infection on entrance into military service. There is therefore no suggestion that their military service (in theaters of war not foci of

leprosy) is in any way connected with the development of the disease.

The situation at the present time in respect to veterans of World War II is similar. Eleven cases have occurred, or existed before entrance into military service, in native-born persons. All but 1, to be discussed later, were born in foci of the disease in this country. The important consideration epidemiologically is whether the future will be like that of the Spanish-American or of World War I.

Cases of leprosy in the three wars according to age at the development of symptoms are shown in Chart 2. Spanish-American War veterans developed the disease at ages ranging from 32 to 66 years, while the age of World War I and World War II veterans is much younger, ranging from 16 to 42 years. These data bear out the suggestion derived from analysis of Chart 1, that veterans of the Spanish-American War, largely from areas not foci of the disease, developed their

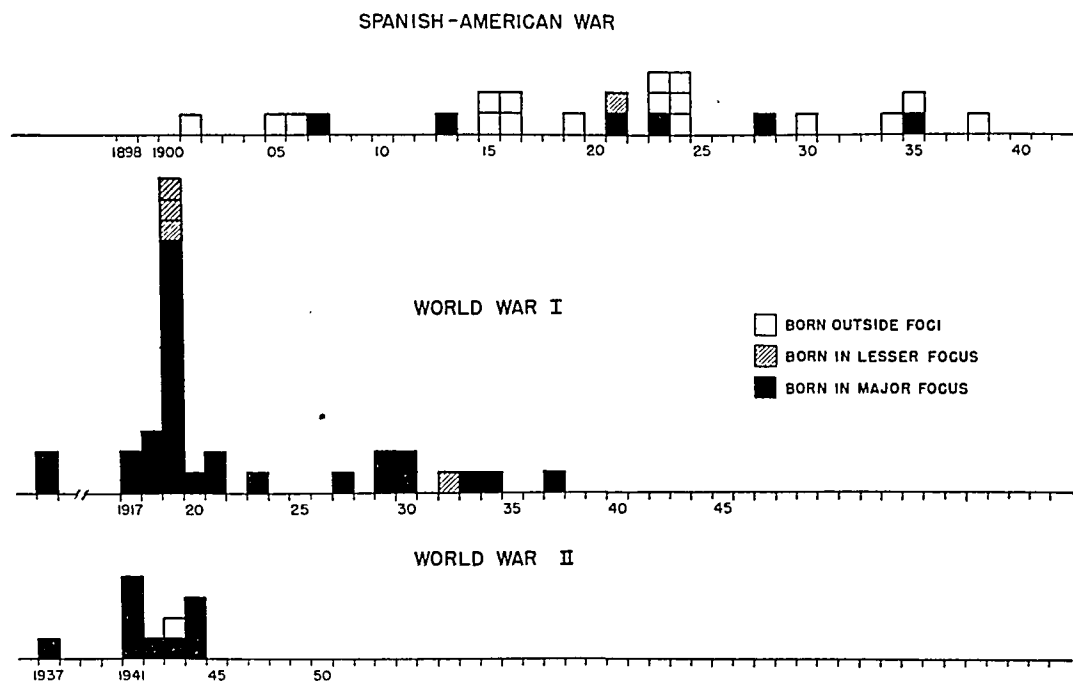


CHART 1.—Leprosy in veterans of American Wars according to year of first symptoms.

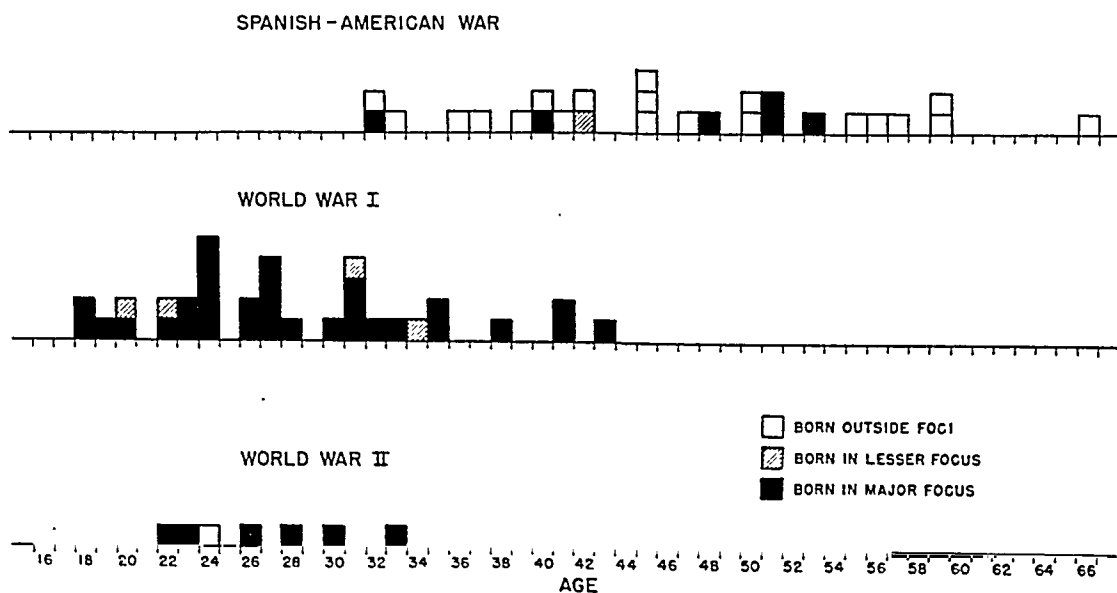


CHART 2.—Leprosy in veterans of American Wars according to age at which first symptoms occurred

infection following initial exposure in adult life; while veterans of World War I and of World War II thus far have developed the disease at much younger ages, suggesting exposure at correspondingly younger ages and in domestic foci as indicated by their place of birth.

available. However, the racial origin would be expected to correspond to the racial stocks of the majority of cases admitted from these foci.

Chart 5 shows the place of birth of veterans of World War II who have, up to this time, been reported as cases of

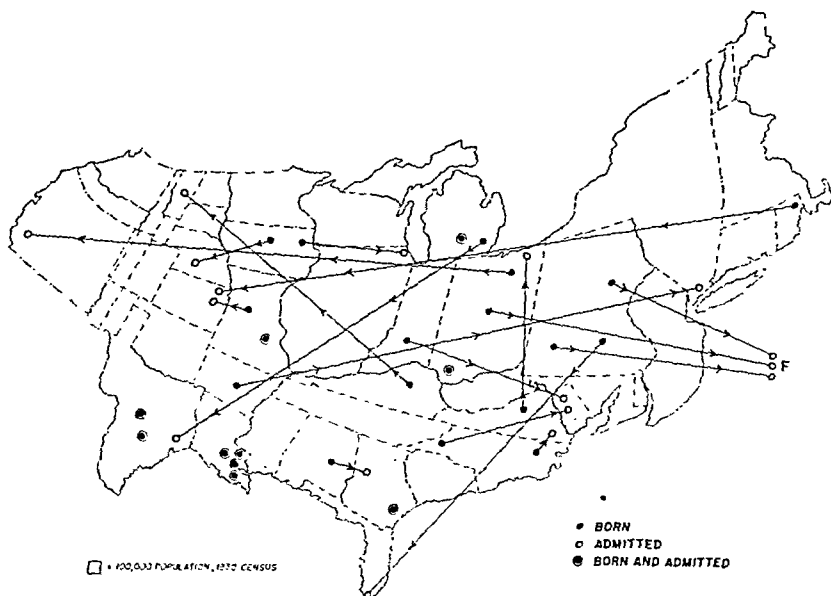


CHART 3.—Leprosy in veterans of Spanish-American War by place of birth and admission.

**REGIONAL AND RACIAL DISTRIBUTION.** Chart 3 shows native-born Spanish-American War veteran patients by place of birth and place from which they were admitted to the National Leprosarium.<sup>13a</sup> Information on racial origin is available for relatively few. It may be pointed out that 2 of the 3 cases born in Ohio and 1 in Iowa are of German descent. It is of some interest that 6 other cases<sup>3</sup> of German descent appear on the records of admissions to the National Leprosarium from these and adjacent North Central states. No information is available on familial relationships.

Veterans of World War I are similarly shown in Chart 4. All patients were born in states which are foci of the disease, though a number were admitted to the leprosarium from other localities. Information on the descent of relatively few is

leprosy. Of the 3 from California, 2 are Japanese and 1 a native American. Of the 4 cases from Texas, 3 are Mexican and 1 American. Of the cases from Louisiana, 3 are given as American. The one patient born outside of known recognized foci is Jewish and from a city in Illinois where 2 Jewish patients born in foreign countries had previously been recognized. No information is available on relationships.

**RACIAL AND FAMILIAL.** In respect to racial descent, World War II cases correspond to other admissions from the same areas, except that a higher proportion are classified as "American." New Orleans has furnished in the past a number of cases of German descent and the name of the World War II veteran from New Orleans suggests German origin. The majority of patients from Louisiana have been French.<sup>14</sup> The name of one World War

II veteran from Louisiana is French, although listed as American. This patient gives a history of an uncle and 2 cousins with leprosy. We have in addition a record of another case in Louisiana of the same name whose father and mother both bear the same surname (indicating inter-

relationship). This surname is the same as that of 6 cases which have occurred in the New Brunswick focus of leprosy. Incidentally 2 other World War II veterans, 1 born in the Philippines and the other in Hawaii, give a history of leprosy in relatives.

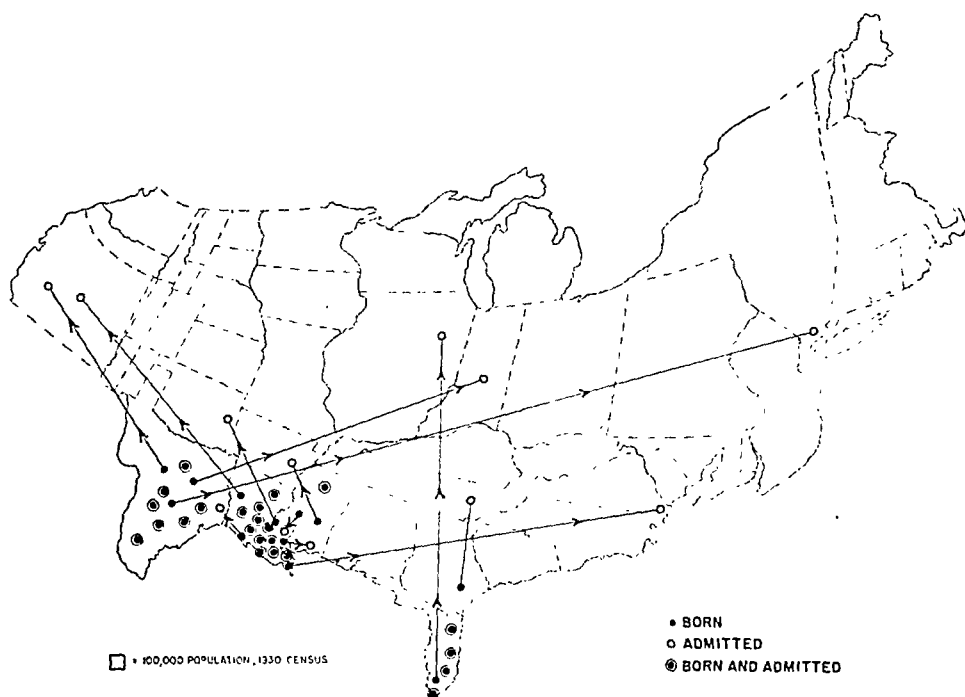


CHART 4.—Leprosy in veterans of World War I by place of birth and admission.

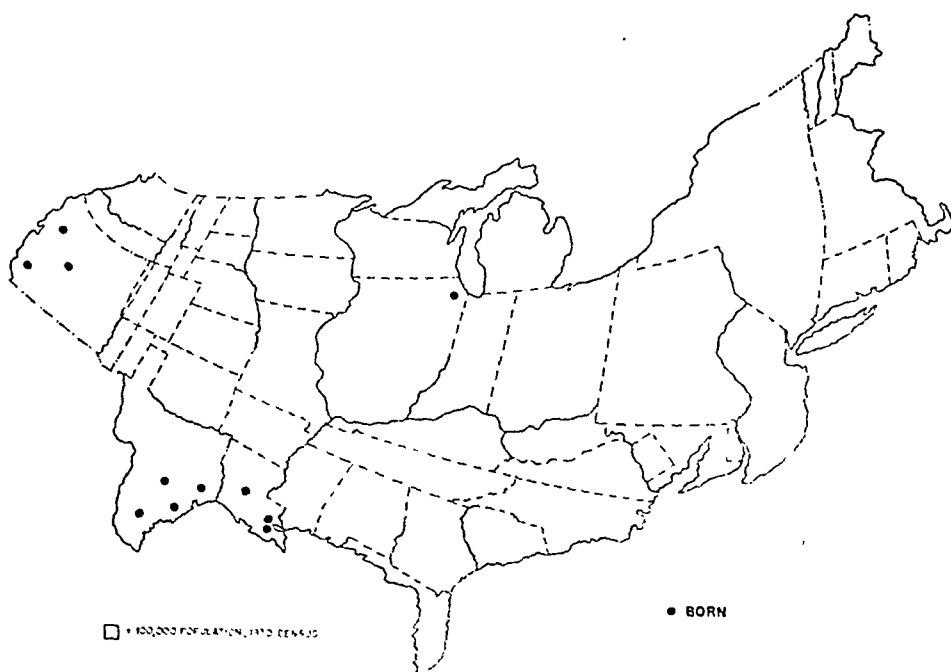


CHART 5.—Leprosy in veterans of World War II as of 1946 by place of birth.



With the passage of time, increasing difficulty is to be expected in establishing racial and familial relationships from the perfunctory data usually appearing on case histories. What with the change in later generations of persons of foreign descents to what is in essence American, the anglicizing of distinguishing family names and other such factors, the continued study of familial relationships must of necessity be carried out by persons familiar with these factors and through direct interview with the persons concerned. Leprologists have repeatedly emphasized the difficulty or impossibility of obtaining information by interview because of reluctance to reveal information concerning the presence of this "unclean disease" in the family. On the contrary, it has been our experience that as soon as it is made clear that the reason for such inquiry is the study of leprosy and not the "apprehension of lepers," members of families where leprosy has occurred are willing and often eager to coöperate. Out of several hundred such families, located in one way or another, and approached with no authoritative introduction, only two have declined to answer questions concerning their family histories. A very old man, whose family had been literally obliterated by leprosy, evidently could not bring himself to talk about it. He dismissed us in his living room with the statement that it was "a closed book" walked out and closed the door. The other was a very intelligent gentleman who did not hesitate to give details of his own case but courteously stated that while appreciating the importance of the study, he could not give information about his family; because

his family history contained certain things that he did not feel he could reveal, however confidentially the information might be treated. We are inclined to believe those "things" were not particularly associated with the presence of leprosy in the family.

**Summary and Conclusions.** This study of the regional, racial, and familial relationships in veterans of American wars suggests that in the immediate years to come an appreciable number of cases of leprosy may be expected to occur among the veterans of World War II who served in theaters of operations which are foci of leprosy.<sup>16c,20</sup> It further suggests that study of these cases in relation to other instances of leprosy occurring in the United States, will aid in determining the relative value to be assigned to "prolonged and intimate exposure" and to familial susceptibility as factors in the epidemiology of the disease. More specifically, there is need for a continued study of the leprosy still to develop among veterans of World War II. Based on experience, observations should be continued until about 1982.

The evidence at hand would indicate that in large part the circumstances associated with the Spanish-American War will be duplicated. The history of exposure will tend to be definitive rather than prolonged and intimate. The roster of patients will not be limited to residents of recognized foci in the South but will include natives of other states. The racial and familial pattern will reflect the selectivity previously exhibited in the occurrence of the disease in those areas.

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# BOOK REVIEWS AND NOTICES

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**OCCUPATIONAL DISEASES OF THE SKIN.** By LOUIS SCHWARTZ, M.D., Med. Director, U. S. Public Health Service; LOUIS TULIPAN, M.D., Clinical Prof. of Dermatology and Syphilology, New York Univ. College of Medicine; SAMUEL M. PECK, B.S., M.D., Dermatologist, Mt. Sinai Hosp., New York. 2nd ed. Pp. 964; 146 ills.; 1 color plate. Phila.: Lea & Febiger, 1947. Price, \$12.50.

The first edition of this book was reviewed in the *AMERICAN JOURNAL OF THE MEDICAL SCIENCES*, 199, 572, 1940. In the present edition, to the original two authors a third has been added, Dr. Samuel Peck, former associate of Dr. Schwartz in the Dermatoses Section, United States Public Health Service. In his own right, Dr. Peck is an outstanding authority in dermatology.

This edition contains the best features of the first, plus descriptions of new chemicals, new methods of manufacture, many developed during the war, and of new cutaneous hazards to workers engaged in their manufacture, as well as to the public who use products containing these irritants. The new edition also shows evidence of definite attempts to overcome the shortcomings, few as they were, of the original edition. All this has occasioned some increase in the size of the book without, however, making it too large for ready handling.

In such a book there are bound to be some repetitions and minor omissions; for example, the patch test is described more or less along similar lines on pages 54 ff. and 302 ff. but with probably some unintentional variations in technic. Erysipeloid is described on pages 619 ff. and 796 ff. Chapters II and XLVI could be combined with profit. On the other hand, there is no discussion of BAL (British Anti-Lewisite) for arsenical and other metal intoxications, nor is there any mention of the use of penicillin in erysiploid. Penicillin as an occupational hazard to physicians, which is omitted, should also be mentioned.

*Occupational Diseases of the Skin* must be easily accessible to anyone who has anything to do with Industrial Dermatology, for it is the American standard, authoritative, en-

cyclopedic source book for the specialist as well as for all physicians concerned with problems of the skin and industry.

H. B.

**RADIOACTIVE TRACERS IN BIOLOGY.** By MARTIN D. KAMEN, Assoc. Prof. of Chemistry, Edward Mallinckrodt Inst. of Radiology, Washington Univ., St. Louis, Mo. Vol. I. Pp. 281. New York: Academic Press, 1947. Price, \$5.80.

This most timely and informative book deals with many different aspects of biological research with radioactive methods, and constitutes an excellent review of the possibilities in the field. The book covers the fundamental properties of atomic nuclei and the source of radioactivity, the production of radioactive isotopes, the physical nature of radiations from tracer atoms, the basic instruments necessary for radioactive assay, and the different approaches used in the fields of biology, biochemistry, and physiology.

The 3 major isotopes of biological research— $H^3$ ,  $C^{14}$  and  $C^{14}$ —are given thorough consideration in methods of assay and application. Even type problems and results are discussed. Details of preparation and application of other radioactive elements of biological importance are also reviewed. The book closes with an interesting chapter on radiation therapy and other medical applications of radioactive techniques. The field of radioactivity as applied to biological research is well covered, and recent developments are often thoroughly considered.

I. Z.

**METHODS OF VITAMIN ASSAY.** Prepared and edited by the Association of Vitamin Chemists, Inc. Pp. 189. New York: Interscience Publishers, Inc., 1947. Price, \$3.50.

The scope of the book is limited. Only such methods are included as have been successfully applied to a variety of foods or other materials by several committee mem-

bers. Selected references to other vitamin methods are listed.

There is a chapter on sampling. The methods given in detail concern Vitamin A, carotene, thiamine, riboflavin, niacin and ascorbic acid.

The chapters have the following subtitles: Preliminary considerations (properties, etc.), methods available, descriptions of the best methods, application of methods, literature cited. In the descriptions of methods many valuable paragraphs are given concerning equipment, reagents and procedure.

D. W.

**DISEASES TRANSMITTED FROM ANIMALS TO MAN.** By THOMAS G. HULL, PH.D., Director, The Scientific Exhibit American Medical Association. 3rd ed. Pp. 571; 75 ills. Springfield, Ill.: Charles C. Thomas, 1947. Price, \$10.50.

ALTHOUGH much of its material is available through other sources, this book provides a valuable correlation between human diseases and those of lower forms. The book is well written and easily read. The historical backgrounds of the various diseases are excellent, and the summaries at the end of every chapter are useful.

As is frequently the case where a book is the work of many contributors, some chapters—such as that on ornithosis—are very helpful; whereas others—such as that on fungus diseases—are mere summaries and of little practical value. In the present edition, tsutsugamushi disease, lymphocytic choriomeningitis, and several other diseases have been added. Of particular value from a public health standpoint are the interesting discussions of this rôle played by each animal in the spread of disease.

A. R.

**VASCULAR DISORDERS OF THE LIMBS.** By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician-in-Charge of Department of Clinical Research, Univ. College Hosp., London. 2nd ed. Pp. 118. New York: Macmillan, 1946. Price, \$2.25.

THIS edition of Lewis' book includes additions to the chapter on therapy of peripheral arteriosclerosis and thromboangiitis obliterans. A chapter on arteriovenous fistulae has been added, and Raynaud's phenomenon is

discussed at greater length. Lewis' description of his technique of studying patients with peripheral vascular diseases makes this book of fundamental importance to all who are interested in the pathologic physiology of the peripheral blood-vessels. Curiously, despite the title, there is nothing on the common diseases of the veins.

M. N.

**PRACTICAL ANESTHETICS.** By J. ROSS MACKENZIE, Univ. of Aberdeen. 2nd ed. Pp. 172; 71 ills. Baltimore and London: The Williams & Wilkins Co., 1946. Price, \$3.00.

THIS simple text has been revised throughout. The pre-anesthetic examination is described in more detail and a rational approach to premedication of the patient on a metabolic basis is given. There is additional information on trilene for anesthesia. The chapter on intravenous anesthesia has been enlarged and a section on brachial plexus block added. The value of this text is questionable. There is little physiology or pharmacology. The volume is too scant in coverage to be helpful. It must be admitted, however, that this edition is vastly improved over the 1st.

R. D.

**ROENTGEN INTERPRETATION.** By GEORGE W. HOLMES, M.D., Board of Consultation, Massachusetts General Hospital; Clinical Professor of Roentgenology, Emeritus, Harvard Medical School; and LAURENCE L. ROBBINS, M.D., Radiologist-in-Chief, Massachusetts General Hospital. 7th ed. pp. 398; 266 ills. Phila.: Lea & Febiger, 1947. Price, \$7.00.

THIS book has become a standard text for those who teach radiology to medical students. Likewise, it is a small text that is used by many radiologists. The authors, in an admirable way, have brought the subject of radiology up to date.

In spite of the difficulty of getting paper these days, the publishers used a good calendered paper, resulting in good Roentgen illustrations. The print is very easy to read, and the composition of the book is agreeable to the eyes. This is the type of book that should be on the shelf of everyone interested in radiology and medicine in general.

E. P.

**THE MEDICAL CLINICS OF NORTH AMERICA.** Philadelphia No. Pp. 282; 24 ills. Philadelphia: W. B. Saunders, 1946. Price, \$16.00 a year.

THIS number is divided into 2 major sections: The first portion is a symposium on the treatment of common cardiovascular conditions. It is a concise, specific review of current trends, in the therapy of such disorders as bacterial endocarditis, coronary artery disease, congestive heart failure, and even pulmonary embolism and peripheral vascular disease.

The second half is a timely symposium on clinical pathology, including the significance of laboratory methods in the diagnosis of syphilis, anemias of childhood, hemorrhagic diseases, lymphadenopathies, bronchogenic carcinoma, and hepatic dysfunction.

W. J.

**LEHRBUCH DER GYNAEKOLOGISCHEN DIAGNOSTIK.** By DR. W. NEUWEILER. Pp. 474; 406 ills., 16 in color. Berne: Hans Huber, 1946. Price, Schw. Fr. 58.

THIS book contains 2 principal sections. The first describes the technique of gynecologic history-taking and examination. The second, and much the longer section, discusses the physical findings and diagnosis of the pathologic disorders that may arise in the female genital organs. Functional disorders are not included, except for brief chapters on certain aspects of sterility, and on pelvic pain of extragenital origin.

The section on technique is well done, but offers little that is not already recognized as standard practice in this country. American gynecologists will probably take exception to the author's recommendation of laminaria tents, long outmoded here, for dilating the cervix preliminary to punch-biopsy or curette-biopsy of the endometrium.

Much the more valuable part of the book is the section on pathology. This is profusely and, in general, well illustrated with photographs of the lesions under discussion, including a number of excellent color prints. Under the circumstances, it is unfortunate that the quality of paper on which they have been reproduced could not be better.

The book will be of particular value to gynecologists, but can be recommended to all diagnosticians whose work touches this field.

C. B.

**HYPOMETABOLISM.** A Clinical Study of 308 Consecutive Cases. By **ESBEN KIRK**, M.D., Holstebro District Hospital, and **SVEN ANCHER KVORNING**, M.D., Univ. of Copenhagen. Pp. 40; 4 figs.; 13 tables. Copenhagen: Einar Munksgaard, 1946. Price, Dan. Cr. 7.25.

THIS is a small brochure giving a detailed clinical study of 308 cases of "hypometabolism" admitted to the Medical Department of the Holstebro District Hospital in Denmark. Exhaustive analyses of symptoms presented in the form of tables are given, together with a chapter dealing with the effect of thyroid administration in this condition. The brochure should be of interest to the specialist.

W. S.

**DENTISTRY, AN AGENCY OF HEALTH SERVICE.** By **MALCOLM WALLACE CARR**, D.D.S., and 19 Contributors. Pp. 210. New York: Commonwealth Fund, 1946. Price, \$1.50.

THIS comprehensive review of Dentistry in the United States emphasizes Dentistry's position as a health service profession and points out the many interrelationships between Dentistry and Medicine and the position of these professions in the changing social order. Public Health and social workers who desire a comprehensive overview of Dentistry will find the Summary and Conclusion chapter extremely valuable.

The chapter on Hospital Dental Service is particularly informative. Carr emphasizes the important position of Dentistry as one of the essential hospital health services. These dental services include: care of the hospital patient in whom oral infection may be an etiologic or aggravating factor in systemic disease, emergency dental or surgical treatment for relief of pain, and the care of the ambulatory patient referred from the other out-patient clinics.

Regular dental examination immediately after admission is particularly desirable. Routine oral hygiene care for the hospital patient can be done largely by the dental hygienist under supervision. Special oral hygiene service should be administered before operation for all surgical patients and antepartum patients. The hygienic state of the mouth of the surgeon, nurses, and interns is also important.

Since oral health service occupies a stra-

getic position in the practice of medicine and surgery, a dental representative should be on the medical board. According to Carr, medical faculties and staffs are too frequently indifferent to the principles of oral pathology as related to systemic disease and the clinical aspects of diseases of the mouth.

The New York Academy of Medicine should be complimented for their sponsorship of this volume and their recognition of Dentistry as one of the health service professions.

L. B.

**THE PROBLEM OF FERTILITY.** Edited by EARL T. ENGLE. Pp. 254. Princeton Univ. Press, 1946. Price, \$3.75.

THIS small volume contains a collection of 16 papers presented and discussed at the February 1946 Conference on Fertility of the National Committee on Maternal Health. The papers represent recent studies of ovulation and spermatozoal physiology in various animals by authorities in the field of animal husbandry. As the discussions are contributed by recognized students of human fertility, unique and stimulating views of related aspects of a common problem are achieved.

C. B.

**THE PERSONALITY OF THE PRESCHOOL CHILD.** By WERNER WOLFF, PH.D., Professor of Psychology, Bard College. Foreword by MARY FISHER, PH.D., Chairman, Dept. of Child Study, Vassar College. Pp. 241; 118 figs. New York: Grune & Stratton, 1946. Price, \$5.00.

THIS study in the realm of "depth psychology of childhood," is by a pioneer, and, though the subject remains largely in the experimental and controversial stage, the work is stimulating. Insisting the child must not be judged by adult standards, that the behavioristic and analytic schools do not offer the best methods of approach, the writer considers "The Child's Search for His Self," under the headings of Observation, Experimentation and Theory.

The chapters are: The Mind of Child and Adult; The Emotion of Child and Adult; The First Characteristics of Social Life; The Child's Concept of Reality; The Preschool Child as an Individual; The Child's Feeling of Security; Intelligence in the Preschool Child; Projective Methods for Expressive Behavior of Preschool Children; Principles

of Children's Art; Child and Adult: The Educational Bridge Between Two Worlds; Methods in Child Psychology.

The children of this study were from 3 to 5 years old. Much importance is attached to measuring the subject's degree of configuration or rhythmization, his rhythmic quotient, or R.Q. A child was asked to draw the picture of a man. Numerous measurements were made in the 3 parts, head, trunk and legs. Working then with the number of proportions and the given elements, by a method that would require a long detailed explanation, the end result is the child's R.Q. The I.Q. and R.Q. are not necessarily in agreement. But, "If the degree of I.Q. is similar to that of R.Q., this seems to indicate a unified pattern of personality."

The writer endeavors to support his theories by citing 2 historic characters: Dostoevski, an epileptic, whose seizures were attended by an enormous extension of his ego—time and space were greatly expanded. And Rousseau, whose childhood punishment led to perverted sexuality.

N. Y.

**THE ESSENTIALS OF OBSTETRICS AND GYNECOLOGY.** By WILLIAM ALBERT SCOTT and H. BROOKFIELD VAN WYCK, University of Toronto. Pp. 390; 126 ills. Philadelphia: Lea & Febiger, 1946. Price, \$5.50.

THIS attractively published book is an attempt to bridge the gap between student manuals of Obstetrics and Gynecology on the one hand, and textbooks on the other. It aims to compress the presentation of the subject into a brief treatise without resort to the sketchy outlines common to the crammer's compendiums.

There is a real need for such an introductory treatise of obstetrics and gynecology, but the writing of it must inevitably present many difficulties. The authors of this book have succeeded admirably in covering the practical aspects of the subject. In the Reviewer's opinion, however, it is to be doubted whether emphasis on practical aspects provides the ideal approach for the medical student in his introduction to this field. For example, the authors might well have omitted discussions of various forms of obstetric analgesia in favor of a fuller discussion of the physiology of pregnancy. Similar contrasts might be cited, together

with a failure to "orient" the beginner on the relation of his new field to the disciplines with which he has already been made familiar, and to the field of medicine in general.

The book is beautifully illustrated, but here again, the teachers who scan it will note that the problems illustrated are too frequently those which would interest the practitioner or advanced student, rather than those in which the neophyte needs visual aids.

C. B.

**WHAT IS HEART DISEASE.** By WILLIAM HYATT GORDON, Head of the Medical Section, Lubbock Memorial Hospital and Clinic, Lubbock, Texas. Pp. 114; 10 figs. New York: Grune & Stratton, 1946. Price, \$2.50.

This small book describes simply, briefly and clearly the anatomy and function of the normal heart, and the abnormalities that develop as the result of the various common types of heart disease. The principles of treatment are explained. It is well suited to educate the patient who has or thinks he has heart disease.

C. K.

#### GASTROENTEROLOGY IN GENERAL PRACTICE.

By LOUIS PELNER, M.D., Associate Attending Physician, Greenpoint Hospital; Associate Visiting Physician, Brooklyn Cancer Institute; Adjunct Physician, Beth Moses Hospital, Brooklyn, N. Y. Pp. 285; 108 figs. Springfield, Ill.: Charles C. Thomas, 1946. Price, \$7.50.

This is an up-to-date, abbreviated textbook on clinical gastroenterology for the practitioner and the student. It is written in a simple, terse style and is exceedingly well illustrated. In covering the more important aspects of his subject, the author has made use of tables, diagrams, diet lists, differential diagnosis charts and roentgenologic illustrations in such fashion as to cover a mass of data in a short space. He has assembled the current opinions of the leader in the field of gastroenterology and has wisely chosen to present both sides of controversial issues. Some interesting chapters on the psychosomatic aspects of gastrointestinal disease again remind us of the importance of this phase of medicine. He has also included sections on biliary and pancreatic disease and his diagrammatic repre-

sentation of the pathologic physiology of jaundice is particularly commendable. It should be pointed out, however, that the effectiveness of methionine in liver disease, though apparently proven in the experimental animal and readily accepted by Dr. Pelter, has not yet been demonstrated in man.

S. L.

**OUTLINE OF THE SPINAL NERVES.** By JOHN FAYILL, A.B., M.D., F.A.C.P., Clinical Professor of Neurology, University of Illinois College of Medicine. Pp. 191; 26 figs. Springfield, Ill.: Charles C. Thomas, 1946. Price, \$3.75.

The first 4 parts of this book are an attempt to make available, in compact form, full information on motor function and neurologic analysis of roots, nerves, muscles and movements. These sections of the book are titled successively: I. Roots-Nerves-Muscles, II. Nerves-Muscles-Roots, III. Muscles-Roots-Nerves, IV. Movements-Muscles-Nerves-Roots, so that it is possible, given a disability occurring at any point in the final common pathway, to analyze it with respect to the related elements of innervation. Clinical relationships are given briefly in Part II.

The book contains, in addition, supplementary material on spinal plexuses, electrical testing, causalgia, neuritis, low back pain and muscle disorders. Charts on segmental and peripheral sensory innervation are included.

The book presents in readily available form a mass of neurologic and anatomic data which cannot be satisfactorily found in any other single source. Its usefulness to the clinician grows with usage.

J. W.

**MILITARY NEUROPSYCHIATRY.** The XXV Volume of the Association for Research in Nervous and Mental Disease. Edited by FRANKLIN G. EBAUGH, HARRY C. SOLOMON, M.D., THOMAS E. MUMFORD, Jr., M.D., with 47 Contributors. Pp. 366; 34 ills.; 48 tables. Baltimore: Williams & Wilkins, 1946. Price, \$6.00.

In this study there is strict adherence to the original plan of discussing but 1 subject. Among the more important chapters are: Changing Concepts of Psychoneurosis in Relation to Military Psychiatry. Neurotic Reactions in Psychopaths (Hystero-Mal-

ingering). Psychiatric Contrasts in the Two World Wars. Emotional Problems of Demobilization. The Problem of the Discharged Neuropsychiatric Patient. Concerning Combat Exhaustion. The Importance of the Emotional Outlet in Psychotherapy. Psychopathology and Group Therapy. Psychotherapy in a Convalescent Naval Hospital. The Therapeutic Rôle of Drugs in the Process of Repression, Dissociation and Synthesis. The Electroencephalogram in War Wounds of the Brain: with Particular Reference to Post-traumatic Epilepsy. Neuropsychiatric Problems of the Veterans Administration. Psychiatric Rehabilitation in Industry. Personality and Psychosomatic Disturbances in Patients on Medical and Surgical Wards: A Survey of 450 Admissions. The Development of Group Psychotherapy in Military Setting. Modification of the Rorschach Method for Large Scale Investigations.

After hysterical manifestations were carefully excluded, malingering was mostly an effort of the psychopath. Merono's Psychodrama, a group therapy agent, was helpful in the psychiatric convalescent hospital. The tedious Rorschach test was provided with a short-cut, by projecting the inkblots as colored slides on a screen; negativistic subjects, unable to do themselves justice under the individual test, often felt free to write down their descriptions. A subject accorded much discussion was fatigue, and results obtained at the Swarthmore Convalescent Annex of the Philadelphia Naval Hospital, were gratifying. There, much work is done in a very complete photographic laboratory, in the assembling and tearing down of motors, carpentering, etc. Needless to say the Weir Mitchell rest cure is no longer employed. This book is valuable for permanent reference, and contains many case studies, with thorough analyses of important neuropsychiatric problems. N. Y.

PARENTERAL ALIMENTATION IN SURGERY, WITH SPECIAL REFERENCE TO PROTEINS AND AMINO ACIDS. By ROBERT ELMAN, M.D., Associate Professor of Clinical Surgery, Washington University School of Medicine, St. Louis, Mo. Pp. 284; 31 figs.; 20 tables. New York: Paul B. Hoeber, 1947. Price, \$4.50.

THE title does Dr. Elman injustice, for he has presented a comprehensive review of

the deficits which result from the inability to ingest adequate food, of the indications for the parenteral administration of various nutritional substances and the physiologic results of their administration. This is a work which should be helpful to everyone interested in nutrition and of considerable value to all clinicians.

In spite of the author's primary interest in parenteral feeding, to which field he himself has made important contributions, he has retained his good clinical judgment and warned those of us who may have become too enthusiastic about this method of supplying nutritive elements to our patients that "Parenteral alimentation should always be considered as a *temporary expedient* during the course of surgical care, designed to lead as rapidly as possible to a condition in which the patient can take the required fluid and food elements by mouth."

One of the greatest values in a monograph of this type is to make evident the limitations of our knowledge of the field. Undoubtedly there will be those who will be stimulated to explore further in an attempt to solve the many problems of nutrition which are presented but not yet solved.

The Reviewer recommends this monograph highly. I. R.

#### MODERN DERMATOLOGY AND SYPHILOLOGY.

By S. WILLIAM BECKER, Clinical Professor of Dermatology, University of Chicago, and MAXIMILIAN E. OBERMAYER, Clinical Professor and Chairman, Department of Dermatology, University of Southern California. 2nd ed. Pp. 1017; 461 ills.; 17 full color plates. Philadelphia: J. B. Lippincott, 1947. Price, \$18.00.

In the 1st edition of this volume (1940) an attempt was made to produce a modern text on Dermatology and Syphilology which would be especially useful not only to undergraduate medical student and practitioner but also to postgraduate students and specialists. Innovations in style of presentation, arrangement, and a special feature of explanatory material at the beginning of each chapter under the heading, "Orientation," made the 1st edition of this book a unique contribution.

This 2nd edition, in general, continues the original program. It is a rather cumbersome volume physically, a fact which belies the informal presentation of the material it



contains. It is printed in easy-to-read type in double columns, and is properly illustrated with usually excellent photographs in black and white, or in color (painted). (The only real exception is a copied illustration which is poorly reproduced, Figure 284-A. The original from which it is taken is good.) Several of the colored illustrations are from commercial brochures. Aside from their excellence, they suggest the prominent rôle the pharmaceutical houses are playing in medical research and teaching.

The bibliography is useful, well arranged and selected. Most of the titles are in English.

Certain sections are exceptionally well prepared, reflecting the special interests of the authors, viz: Pigmentation, Lupus Erythematosus; Leprosy; Neurodermatoses and Tropical Diseases. Syphilis, on the other hand, is presented on the whole in a conventional manner.

There are but few criticisms one might make of this edition of Becker and Obermayer's text. It is desirable to point out that commercial pharmaceutical preparations are given undue recommendation for various dermatoses on the one hand, and others now in fashion are omitted, such as the so-called "antihistamine" drugs (Benadryl and Pyribenzamine). This may be due to the fact that at the time of publication, these preparations were not sufficiently evaluated to be incorporated. While adequate warning is issued relative to the dangers of sulfonamides locally, the same is not true of local penicillin therapy. It is not entirely advisable at the present to recommend Acetarsones for any form of syphilis. Verification tests for diagnosis of syphilis are given too much space, since they have proven of little or no value at the hands of competent investigators.

The Reviewer unhesitatingly recommends this book.

H. B.

**HEPARIN IN THE TREATMENT OF THROMBOSIS.** By J. ERIC JORPES, M.D., Reader in Biochemistry, The Caroline Institute, Stockholm, Sweden. 2nd ed. Pp. 260; 24 ills. New York and London: Oxford Univ. Press, 1946. Price, \$6.50.

THE first edition of this monograph appeared in 1939 before purified heparin was available in quantity and at the more reasonable price of today. It was being used clinically

to a limited extent. The present edition has a valuable review of the discovery and chemical characteristics of heparin, but the larger portion of the monograph is concerned with heparin in the prevention and treatment of thrombosis.

The occurrence of fatal embolism following operation would seem to be lower in this country than abroad, according to the figures given. At the Mayo Clinic fatal embolism occurred in about 1 in 800 operations, at the Hospital of the University of Pennsylvania in about 1 in 1200. The figures were from a very large series of patients in each clinic but include all major operations, whereas Dr. Jorpes's data are for abdominal operations. In 302 abdominal operations there were 9 instances of embolism in Crafoord's series. In another reported series of patients untreated with heparin a mortality of 10 patients in 1254 cases seems high. This is contrasted with 1266 heparin-treated patients with 5 deaths. For an over-all figure the author states "until recently there occurred 1 death from thromboembolism in every 400 operations."

Your Reviewer feels he should sound a warning against the enthusiasm expressed for heparin as a preventive and therapeutic agent in all instances of thromboembolism. If there are free clots in the veins as occurs in phlebothrombosis, heparin may not prevent embolus, and it is the Reviewer's opinion that ligation should be resorted to. Preoperative ligation in certain selected cases is a safer prophylactic measure than heparin and less costly. Early ambulation may not reduce the incidence of thrombosis, but it has reduced the incidence of fatal embolism. Heparin or heparin and dicoumarol are useful in some cases, but the surgeon's treatment of each individual patient should depend upon his experience and knowledge. No one method now has universal application.

The monograph supports the thesis that once incipient thrombosis has occurred, it is easily diagnosed and that then this condition may be "successfully treated with heparin." A categorical statement of this type is in the Reviewer's opinion not justified. No method now available is universally applicable. The volume is interesting and helpful in many ways and will assist in further formulating more definite plans of action. It is not the last word on the subject.

I. R.

## NEW BOOKS

*An Approach to Social Medicine.* By JOHN KERSHAW, M.D. (Lond.), D.P.H., Medical Officer of Health, Accrington. Pp. 329. Balt.: Williams & Wilkins, 1946. Price, \$4.50.

*Proceedings of the 11th Annual Convention of the National Gastroenterological Association.* Held in New York, June, 1946. Edited by SAMUEL WEISS, M.D., F.A.C.P., D.Sc. Pp. 187; ills. New York: Medical Authors' Pub. Co., 1947. Price, \$2.50.

*Rocky Mountain Conference on Infantile Paralysis.* By VARIOUS AUTHORS. Introduced by JAMES J. WARING, M.D. Pp. 199; ills. Denver: Univ. of Colorado, School of Medicine and Hospitals, 1946. No price given.

*The Pathology of Traumatic Injury. A General Review.* By JAMES V. WILSON, M.D., M.R.C.P. Lond., Pathologist to Harrogate and District General Hosp., and Royal Bath Hosp., etc., D.A.D.P., Malta Command, 1940-1943. Pp. 192; 61 ills. Balt.: Williams & Wilkins, 1946. Price, \$6.00.

*The Causation of Appendicitis.* By A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S., Prof. of Surgery, Univ. of Bristol. Pp. 79; 4 figs. Balt.: Williams & Wilkins, 1946. Price, \$2.50.

*The Diagnosis and Treatment of Diarrheal Diseases.* By WILLIAM Z. FRADKIN, A.B., M.D., Physician-in-Charge of Colitis Clinic, Jewish Hosp. of Brooklyn. Pp. 254; 113 ills. New York: Grune & Stratton, 1947. Price, \$6.00.

*Medical Addenda. Related Essays on Medicine and the Changing Order.* The New York Academy of Medicine. Pp. 156. New York: Commonwealth Fund, 1947. Price, \$1.75.

*Dermatologic Clues to Internal Disease.* By HOWARD T. BEHRMAN, M.D., Ass't. Clinical Prof. of Dermatology, New York Univ. Pp. 165. New York: Grune & Stratton, 1947. Price, \$5.00.

*Methods of Diagnosis.* By LOGAN CLENDENING, M.D., F.A.C.P., Late Prof. of Clinical Medicine and History of Medicine, Univ. of Kansas, and EDWARD H. HASHINGER, M.D., F.A.C.P., Prof. of Clinical Medicine. Pp. 868; 143 ills. St. Louis: C. V. Mosby, 1947. Price, \$12.50.

*Paravertebral Block in Diagnosis, Prognosis, and Therapy. Minor Sympathetic Surgery.* By FELIX MANDL, M.D., F.I.C.S., Prof. of Surgery, Hadassah Univ. Hosp., Jerusalem. Translated by GERTRUDE KALLNER, M.D., Foreword by MAX THOREK, M.D., F.I.C.S. Pp. 330; 19 figs. New York: Grune & Stratton, 1947. Price, \$6.50.

*La Douleur.* Par le DR. PAUL CHAUCHARD, Director adjoint a l'Ecole paratique des Hautes Etudes. Pp. 126; 10 figs. Paris: Presses Universitaires de France, 1947. Price not given.

*Atlas of Cardiovascular Diseases. Correlation of Clinical Electrocardiography and Cardiac Roentgenology with Clinical History and Autopsy Findings.* By IRVING J. TREIGER, M.D., Ass't Prof. of Medicine, Univ. of Illinois. Pp. 180; 244 ills., 11 in color. St. Louis: C. V. Mosby, 1947. Price, \$10.00.

*A Bibliographic Classification.* By HENRY EVELYN BLISS. In 4 vols. Vol. 2. Pp. 334. New York: H. W. Wilson, 1947. Price, \$7.50.

*Studies on the Influenza A-Epidemic of January-March, 1941 at Groningen (Holland).* By J. A. R. VAN BRUGGEN, M.D., et al. VII. Institute of Preventive Medicine in Leyden. Pp. 64; 26 ills. Leiden: H. E. Stenfort, 1947. Price, \$2.00.

THE interesting results of the work of a team of Dutch medical men.

## NEW EDITIONS

*The Chemical Composition of Foods.* By R. A. McCANCE and E. M. WIDDOWSON. 2nd ed. Pp. 156. Brooklyn, N. Y.: Chemical Publishing Co., 1947. Price, \$3.75.

*Chemistry and Methods of Enzymes.* By JAMES B. SUMNER, Prof. of Biochemistry, Cornell Univ., and G. FRED SOMERS, Plant Physiologist, U. S. Plant, Soil and Nutrition Laboratory, Ithaca. 2nd ed. Pp. 415. New York: Academic Press, 1947. Price, \$6.50.

*Textbook of Physiology.* By WILLIAM D. ZOETHOUT, Ph.D., and W. W. TUTTLE, Ph.D. 9th ed. Pp. 723; 304 ills.; 6 color plates. St. Louis: C. V. Mosby, 1946. Price, \$4.75.

*Medical Disorders of the Locomotor System, Including the Rheumatic Diseases.* By ERNEST FLETCHER, M.A., M.D. (Cantab.), M.R.C.P., of the Royal Free Hosp., etc. Pp. 625; 262 ills.; 2 color plates. Balt. and London: Williams & Wilkins, 1947. Price, \$11.00.

*A Manual of Fractures and Dislocations.* By BARBARA BARTLETT STIMSON, A.B., M.D., Med. Sc.D., F.A.C.S., Ass't Prof. of Clinical Orthopedic Surgery, College of Physicians and Surgeons, Columbia Univ. 2nd ed. Pp. 233; 98 ills. Phila.: Lea & Febiger, 1947. Price, \$3.25.

*Diseases of the Nervous System. Described for Practitioners and Students.* By F. M. R. WALSH, M.D., D.Sc., F.R.C.P. (Lond.), Physician in Charge Neurological Dept., Univ. College Hosp., London, etc. 5th ed. Pp. 351; 59 ills. Balt.: Williams & Wilkins, 1947. Price, \$4.50.

*A Handbook on Diseases of Children, Including Dietetics and The Common Fevers.* By BRUCE WILLIAMSON, M.D. (Edin.), F.R.C.P. Lond. 5th ed. Pp. 408; 83 ills. Balt.: Williams & Wilkins, 1947. Price, \$4.50.

*Microbial Antagonisms and Antibiotic Substances.* By SELMA A. WAKSMAN. 2nd ed. Pp. 415; 34 figs.; 52 tables. New York: Commonwealth Fund, 1947. Price, \$4.00.

This book has the same number of chapters with the same headings as in the first edition. The subject matter has been somewhat revised but mainly new material has been added. Dr. Waksman has added the important material on the antibiotics which has been published since 1945, especially material on streptomycin and penicillin. This edition is larger by 65 pages and the bibliography contains over 1053 references. The book is enhanced in value and still remains a basic text for those interested in antibiotics.

H. M.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### METHYLTHIOURACIL IN THE TREATMENT OF THYROTOXICOSIS

BY ARNE BARFRED, M.D.

DR. MED. 1STE RESERVELEGE MEDICINSK AFD. B.  
ODENSE, DENMARK

(From Medical Service B, City and County Hospital, Knud Schroeder, M.D., Director)

THE purpose of this paper is to summarize the results achieved in using 4-methyl-2-thiouracil in the treatment of 61 cases of thyrotoxicosis and to report the results of maintenance therapy with the same drug.

Since Astwood<sup>1</sup> in 1943 published the first reports on the use of thiourea in thyrotoxicosis many attempts have been made to synthesize a potent and at the same time a non-toxic drug. The ideal preparation is yet to be found. Methylthiouracil is a Danish contribution to the search for such a drug and was suggested by Prof. K. A. Jensen of the University of Copenhagen in 1944, and has been used clinically in Denmark, on a rather large scale, ever since. Coincidentally, Chapman,<sup>8</sup> and O'Donovan,<sup>11</sup> in England, were trying the same compound but without knowledge of the Danish experiments because of war conditions. There are only a few reports from England upon its clinical value. In Sweden and Norway methylthiouracil has been used to some extent.

The experimental work has been done by Freisleben,<sup>14</sup> and Thyssen,<sup>38,39</sup> in Denmark, and Chapman,<sup>8</sup> in England. It was shown that methylthiouracil had a stronger goitrogenic effect on rats than thiouracil, whereas the toxic effect (lethal dose for mice) was the same. Propylthio-

uracil had 10 times as great a goitrogenic effect as thiouracil<sup>2</sup> but this does not hold true of its antithyroid action in man. The reason for this was recently shown by McGinty<sup>25</sup> who proved that methylthiouracil is not conjugated in human blood while the reverse is true of propylthiouracil, resulting in its partial inactivation. Christensen<sup>9</sup> has also shown that several of the thiouracil derivatives are bound to the plasma proteins in blood. Thirty-five % of methylthiouracil can be recovered by ultrafiltration and only 5% of the propylthiouracil can be so recovered. A practical proof of this is the fact that at present the small doses of propylthiouracil proposed by Astwood,<sup>2</sup> based on the marked goitrogenic effect, are being increased while the methylthiouracil dosage is rapidly diminishing and is nevertheless causing a good antithyroid effect. The doses of these 2 drugs are now nearly equal. The reason, however, methylthiouracil received preference in Denmark was not the greater potency of methylthiouracil but the fact that its manufacture was easier and less expensive.

**Material.** Table 1 gives an impression of the different types of cases. It will be noticed that the ratio of women to men is nearly 4 to 1, which is a little more than that usually seen in Denmark.<sup>36</sup> Of the patients belonging to the old age group,



**Technique.** Since 1944 we have used methylthiouracil at the County Hospital in Odense, but the indications for its use have been somewhat varied. Because of reports on the sensitivity to the drug we at first decided to use methylthiouracil solely for treatment of iodine-resistant cases and, as soon as a good response was obtained, to submit the patients to subtotal thyroidectomy. Later we treated all our cases of thyrotoxicosis with methylthiouracil with the purpose of continuing a maintenance dose if there were no contraindications, such as: (1) intrathoracic goiter, (2) a very large and increasing goiter with pressure symptoms, (3) failure by patients to submit to regular basal metabolism rate control.

The following routine was used: All patients were hospitalized and basal metabolism rate determinations were done twice a week. The pulse rate was recorded daily. The patients had no special diet, some received a few sedatives. The leukocyte and differential counts and a test for urobilin in a 1:10 dilution of the urine were done twice a week. The patients stayed in the hospital, with a few exceptions, until the initial dose of methylthiouracil could be lowered, following a fall in basal metabolism rate, a weight gain, and subjective improvement. Thereafter the patients were followed at 2 to 3 week intervals; later when the basal metabolism rate approached a normal level, the patients were followed at 1 to 2 month intervals. After treatment was discontinued, basal metabolism rate was done every 2 to 3 months; leukocyte and differential counts and tests for urobilin were done at the same time and the patients were urged to report immediately any rash, fever, malaise or sore throat. With few exceptions the patients have willingly followed this routine and have been glad to avoid surgical procedures.

**Results.** The results can be very much clarified if one divides the whole material into 2 separate groups as shown in Table 2.

The first group contains all those patients who previously had experienced a long period of iodine treatment and had become more or less iodine-resistant. As already mentioned, these patients were the first to be treated and, as it was recommended at that time, received a rather large dose (1 gm. of methylthiouracil a day); and later, if they were still resistant to treatment, a still larger dose of the drug was used. It is impossible from the graphs to decide whether the larger doses did help, but it does not seem that they did so in the case which is described later on. (The case with the severe neurologic symptoms described under toxic effects.) From what we now know one would expect some decline in the basal metabolism rate from long-continued treatment with methylthiouracil irrespective of the dosage. It is also evident from the animal experiments that when a certain dosage of methylthiouracil is exceeded the goitrogenic effect does not increase.<sup>39</sup> The same clinical impression is reached by Magnusson.<sup>24a</sup> The largest average doses which were given in the initial period of treatment were 1.2 gm. a day (1 patient had 0.4 gm.; 2 patients had 1 gm.; 2 patients had 1.4 gm.; 1 patient had 2 gm.; 1 patient had 2.2 gm.). Because of these dosages which we now would consider as huge, reactions were very frequent and in some cases even severe, though we did not observe any cases of agranulocytosis in this group. Several authors<sup>19,24,42</sup> have stressed the increase in dosage to be the cause of increased sensitivity. There is no doubt, that more of the patients could have been carried through on methylthiouracil treatment if the patients' tolerance to a smaller dose had been tried. After the first signs

TABLE 2.—RESULT OF METHYLTHIOURACIL TREATMENT WITH SPECIAL ATTENTION TO PREVIOUS IODINE TREATMENT

	No. cases	A Treatment effective	B Treatment partly ineffective	C Treatment discontinued (toxic reaction)	Average daily dose in the initial period (gm.)
Iodine for a long period, previous to treatment with methylthiouracil . . . . .	18	7 (39%)	3	8 (44%)	1.20
No previous iodine . . . . .	43	37 (86%)	1	5 (12%)	0.57
Totals . . . . .	61	44	4	13	

of intoxication had occurred. Table 5 shows that we only did this test in 8 out of 14 cases. We now do it routinely.

The second group contains all those patients who did not receive iodine to any extent before methylthiouracil treatment was commenced, although 3 patients had iodine for a week for diagnostic purposes and responded well. This group is the largest group and received gradually decreasing daily doses during the initial period. The first patients treated received doses as follows: 1 patient 1 gm., 2 patients 0.8 gm., the following 26 patients 0.6 gm. and 5 patients 0.4 gm. The last 3 patients

smaller number of reactions, though it is uncertain if it will reduce the danger of agranulocytosis. The comparison of the results shown in Table 2 and the literature on this subject will be commented upon below.

Nearly all authors seem to agree that prolonged iodine treatment prior to methylthiouracil treatment causes a considerable prolongation of the time required for remission. This has been mentioned by several authors.<sup>1,5,16,24,28,34,44</sup> Others<sup>10</sup> have reported contradictory experiences and have demonstrated that thiourea, combined with iodine or even following previ-

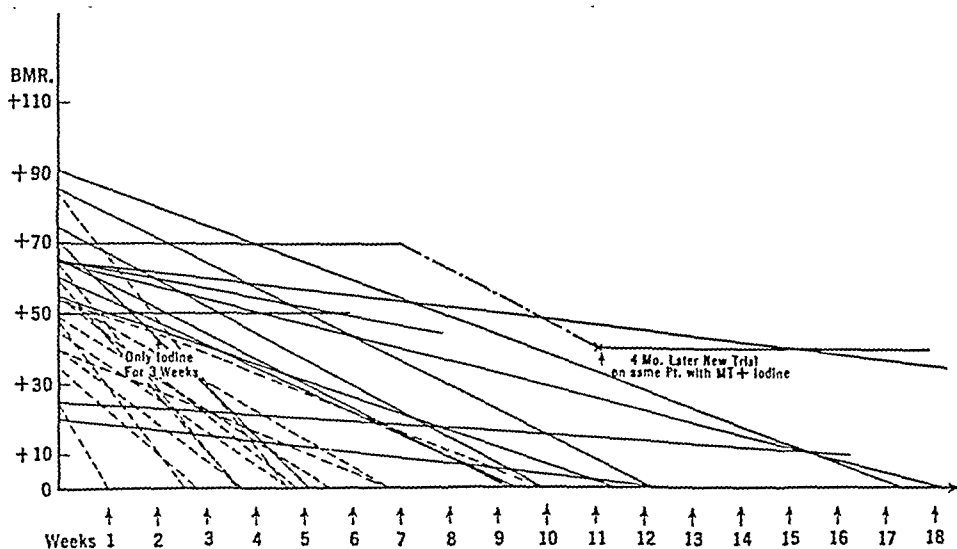


FIG. 1.—14 patients: iodine-resistant cases—other 14 patients: chosen at random, without previous iodine treatment.

have been treated with 0.2 gm. (2 cases) and 0.1 gm. (1 case), and it is our intention in the future not to exceed 0.4 gm. for the first 4 weeks, even if the case has previously been treated with iodine. The average initial daily dose has been 0.57 gm. in this group. The therapeutic results in this group are comparable with other reports on methylthiouracil and give a true picture of what can be expected from this form of treatment. The above-mentioned reduction in dosage has worked satisfactorily and the same experience has been encountered by McGullagh.<sup>27</sup> This reduction in dose will perhaps result in a

ous iodine treatment, does not prolong the treatment; on the contrary, these drugs act as synergists. The possible explanation may be that our cases were iodine-resistant and not ordinary cases of thyrotoxicosis receiving iodine with good effect prior to methylthiouracil treatment. Figure 1 shows 14 cases who were iodine-resistant and who were treated with methylthiouracil following prolonged iodine treatment and who also for some time had iodine and methylthiouracil together. For comparison, the dotted lines represent 14 other cases chosen at random which were not treated with iodine and which had a

similar initial basal metabolism rate. The different rate of response is quite evident from the curves and proves that iodine-resistant cases behave in a special way towards methylthiouracil treatment.

SUSTAINED REMISSIONS AND MAINTENANCE THERAPY. In maintenance therapy our principle has been the following: A gradual decrease in the dosage, not following any set scheme, and then, when the patients have done well for a month or so, on 0.05 gm. a day, withdrawal of the drug usually after an average period of treatment of 5 months.

the mean time for relapses to occur, following cessation of treatment, was 2 months, the maximum time 6 months and the minimum time 1 month.

2. The next sub-group contains all the cases in which an evaluation of maintenance therapy is impossible, either (a) because of preoperative treatment or (b) because of therapy being discontinued as the patient was non-coöperative, or (c) because the treatment is still going on and it is impossible to decide upon the final results. This group is designated, "final evaluation impossible."

TABLE 3.—COURSE OF CASES RESPONDING TO TREATMENT WITH METHYLTHIOURACIL (Corresponds to Group A in Table 2)

		22 patients at present on methylthiouracil therapy				
		Sustained remission after withdrawal of drug	Preoperative treatment	Therapy discontinued (non-co-operative patients)	Reduction in drug dose successful but no attempt to withdraw drug	Sustained remission unsuccessful after reduction or withdrawal of drug
Number of patients:	44	16 Cured 36.4%	4	2 Final evaluation impossible 36.4%	10	12 Relapses 27.2%
Duration of treatment (months)	Mean	5	3	4	6	12
	Max.	10½	4	6	14	17
	Min.	2	½	2	2½	3
Average length of follow-up after withdrawal of drug (months)	Mean	7½				
	Max.	2 in 12				
	Min.	3 in 2½				

Table 3 shows the results of methylthiouracil treatment up to date in 44 patients (Group A) from Table 2, in whom therapy was possible. These cases were divided into 3 main sub-groups:

1. Those who remained in remission even after removal of the drug for an average time of 7½ months, designated in Table 4 as "cured," in the sense that their thyrotoxicosis disappeared during the period in which the symptoms of disease were controlled by methylthiouracil. The criteria for the determination of a remission in this group have included: subjective relief, weight gain, disappearance of the elevated basal metabolism rate and decreased pulse rate. The rather scanty literature on this subject<sup>4,29,35</sup> has demonstrated that the relapses most commonly occur within 2 to 3 months after withdrawal of therapy, but that they may occasionally occur at the end of 6 months or even later. In our cases in sub-group 3,

3. The third sub-group includes all patients who have had relapses after at least 3 months of treatment as the result of withdrawal of the drug; the average total length of treatment being 12 months. The average relapse occurred within 2 months after withdrawal of the drug. Some of these patients may later have a sustained remission, although some have failed twice on withdrawal of the drug. Those patients with 1 year of maintenance therapy not resulting in permanent remission ought to be operated upon. The average dosage of methylthiouracil given to these patients to keep them in remission was a little more than 0.1 gm. a day with a spread from 0.3 to 0.05 gm. This group is designated "relapses."

In Table 4 we have tried to relate the "cured" group with the type of goiter, severity, age, sex, complications, and the duration of the disease, with the thought in mind that thereby we might be able to



TABLE 4.—RELATION BETWEEN COURSE WHEN RESPONDING TO TREATMENT WITH METHYLTHIOURACIL AND THE TYPE OF GOITER, SEVERITY, SEX, AGE GROUP AND COMPLICATIONS AND DURATION OF DISEASE

The number and percentage in:		Each group: This group: Entire material:		Sustained remission after withdrawal of drug		Preoperative treatment		Therapy dis- continued in non-cooperative patients		Reduction in drug successful but no attempt to withdraw		Unsuccessful sustained remis- sion after reduction or withdrawal of drug		22 patients, at present on maintenance dose	
		Incidence in:		Cured		Final evaluation impossible		Final evaluation impossible		30.4%		30.4%		19	
		Percentage in:		30.4%		26.2%		30.4%		30.4%		27.2%		19.7%	
		This table		This table		This table		This table		This table		This table		This table	
		Entire material		Entire material		Entire material		Entire material		Entire material		Entire material		Entire material	
		Total		Total		Total		Total		Total		Total		Total	
Goiter:	Small to moderate	28	36	12	43	33	2	1	8	5	18	14	5	18	14
	Large diffuse	8	13	2	23	15	2	1	1	3	38	23	3	38	23
	Nodular	8	12	2	25	17	1	1	1	4	50	33	4	50	33
Severity:	+	20	31	10	38	32	2	2	7	7	27	23	4	27	23
	++	13	21	4	22	30	2	1	3	4	31	19	1	31	19
	+++	5	9	2	40	22	2	1	1	1	20	11	1	20	11
Sex:	Female	38	51	13	35	25	3	2	9	11	29	22	11	29	22
	Male	6	10	3	50	30	1	1	1	1	17	10	1	17	10
Age group:	18 to 40	22	29	9	41	31	3	3	5	5	23	17	5	23	17
	41 to 50	10	19	5	50	26	1	1	2	2	30	16	3	30	16
	51 to 72	12	18	2	17	11	1	1	3	3	33	22	4	33	22
Complications*		21	38	6	25	16	3	2	7	6	25	16	6	25	16
Duration of disease prior to treatment with drug		Mean	1 year	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months	1 for 24 months
		Max.	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months	1 for 49 months
		Min.	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months	1 for 2 months

+ = 2 cardinal signs and BMR, +15 to +49%; ++ = 3 cardinal signs and BMR, +50%; +++ = 5 cardinal signs and BMR, +50%.

\* Complications: cardiovascular or severe chronic disease such as diabetes.

predict which cases would fall into the "cured" group, and which would belong to the "no lasting cure" group. First of all, it may be pointed out that in starting methylthiouracil treatment we can only expect one-fourth to fall into the "cured" group. This figure is no doubt too small as the use of smaller doses of methylthiouracil will probably reduce reactions and add to the "cured" group, even if some few patients may later relapse.

diseases from which the patients suffered during the time of treatment, whether connected with the thyroid status or not. There were just as many patients who suffered from complications in the "cured" as in the relapsing group, which is rather surprising. Those who were "cured" had only been ill, on the average, for a comparatively short time; however, as there was a great variation between the maximum and minimum duration of the

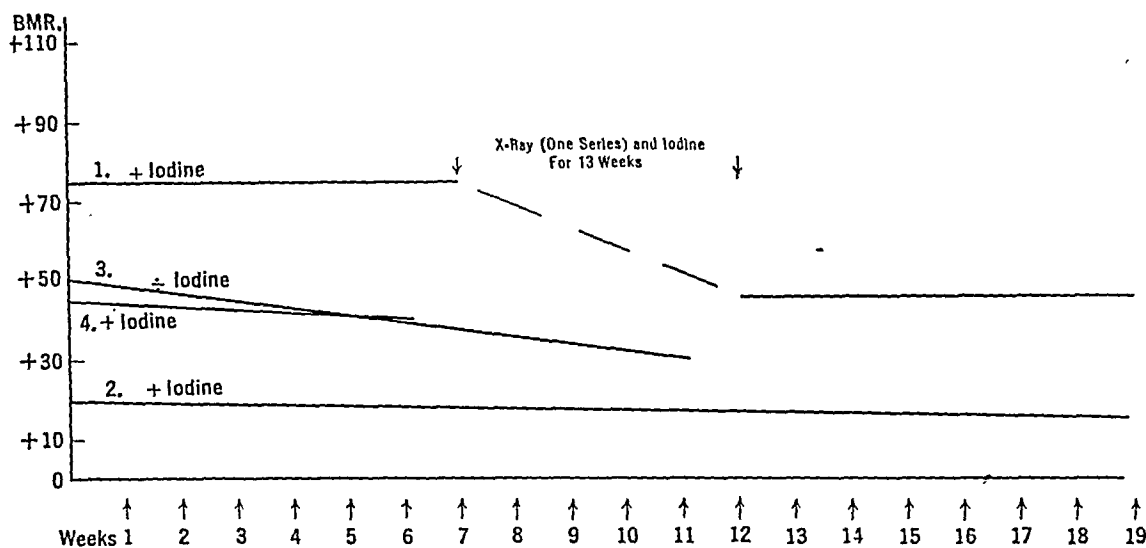


FIG. 2.—4 patients partly resistant to methylthiouracil treatment.

It appears from Table 4 that small to moderate-sized goiters have the highest percentages of cures, while the larger goiters and the nodular goiters show a smaller percentage of cures. Severity of the disease does not seem to have any influence on the results of therapy, but as was pointed out previously, the iodine-resistant cases do not do so well and constitute a separate group. As to sex, relatively more men fall into the "cured" group. In the age groups, there is clear-cut evidence that the younger and middle-aged groups have better results than the old-age group. This is somewhat discouraging as the latter are poor surgical risks due to increasing frequency of cardiac trouble. Even if good surgical risks, these people often state that they are too old for operation. As complications there were considered all the severe

disease in each group, a comparison is only tentative.

The results correspond to those reported in the literature,<sup>5,29,35</sup> though Rose did point out that the complications were chiefly found in the relapsing group.

Of 38 patients, 33 were questioned closely on their ability to work. The average time from the beginning of methylthiouracil treatment until they had resumed full working capacity was 1.2 months.

During therapy we did not notice any significant increase in exophthalmus; on the contrary, in some cases the exophthalmus diminished.

The goiter only increased in size when the basal metabolism rate fell below normal.

Even though the patients were followed carefully during treatment some signs of

myxedema developed in 11 cases although the basal metabolism rate was around 0. In most cases the drug was withdrawn and first reassumed when the symptoms disappeared after 1 to 2 months of observation.

**PARTLY INEFFECTIVE TREATMENT.** Although quite a few authors frankly state that there are no methylthiouracil-resistant cases, 14 of these have been collected in the literature (Table 6), and Rose<sup>35</sup> has described 6 cases following thiouracil. From the reported case histories one has the impression that many of the failures are due to too short a period of treatment. In the cases of Rose *et al.*, the treatment was continued for 7 to 15 months; while the length of our treatment is shown in

those patients who received 0.57 gm.; the latter group had reactions in 47%. It is to be noted, however, that the only case of agranulocytosis occurred in the small dosage group.

A brief protocol of this case of agranulocytosis is as follows:

**Case Reports.** CASE 1. A 59 year old woman had had symptoms of thyrotoxicosis for 11 years which, from time to time, had been treated with iodine, with good results. She had the following complications: hypertension and thyrotoxic heart but without any arrhythmias or cardiac insufficiency. Methylthiouracil, 0.6 gm., was given for 1 month with weekly control of blood and urine, but then, without any warning, the granulocytes suddenly disappeared for 7 days and at the same time she developed the

TABLE 5.—REACTIONS TO METHYLTHIOURACIL

	Iodine for a long period previous to treatment with drug	No long iodine period immediately prior to drug treatment	Totals
Maximum grams per day . . . . .	1.20	0.57	
Average duration of treatment with high doses . . . . .	28 days	20 days	
All—even slightest signs of reaction (% of group) . . . . .	14 (78%)	20 (47%)	34 (56%)
Agranulocytosis . . . . .	0	1	1
Neurologic symptoms (motor-sens) . . . . .	2	1	2
Fever . . . . .	2	9	16
Skin eruption . . . . .	5	8	13
Urobilinuria . . . . .	12	7	19
Dyspepsia . . . . .	6	8	14
Paresthesia . . . . .	1	5	6
Vertigo . . . . .	1	1	1
Leukopenia . . . . .	1	2	3
Absolute lymphocytosis . . . . .	1	1	1
Drug not reported . . . . .	6	4	10
Repeated reaction after a small dose . . . . .	2	3	5
No repeated reaction after drug . . . . .	6	13	19
Transient myxedema during treatment . . . . .	..	..	11

Figure 2. Cases 1 and 2 were certainly not improved in any way in spite of adequate doses. In Case 3 there was a slow fall in basal metabolism rate but no improvement in the general status of the patient. This also applies to Case 4, but we ought to have treated this patient for a longer period.

**REACTIONS TO METHYLTHIOURACIL.** As previously stated, several authors have stressed that the reactions depend upon the quantity of the drug. It is therefore fair to divide the material into 2 groups as in Table 5 in the same way as in Table 2. It is then very evident that the toxicity is much greater (78%) in the group receiving 1.2 gm. of methylthiouracil as an average initial daily dose than in

usual accompanying symptoms. The drug was at once withdrawn, penicillin was instituted, and the patient recovered.

In the group not treated with iodine, the percentage of reactions (47%) while smaller than in the iodine group, was considerable, but in only 5 cases, one-fourth of this group, was it necessary, because of repeated drug reactions, to discontinue treatment.

The high incidence of reactions can be explained by the scrupulous questioning and examination of the patients at each visit. Actually some of the symptoms could have been attributed to intercurrent causes, but, when not proved otherwise, they were attributed to methylthiouracil,

One of the important findings was a positive urobilin test in the urine (the urine being diluted 10 times before the test) which often accompanied other signs of intoxication. When following these patients weekly they were always found to have a negative urobilin test until the signs of intoxication developed. We did not see any cases of jaundice, the blood bilirubin and the Takata-Ara test were normal when tried in connection with a positive urobilin test. Recently it was pointed out by Ehrich<sup>13</sup> that there is a rather high incidence of liver damage in experimental animals when treated with thiouracil and one of the first signs of sensitivity is manifested in the liver. In clinical reports this has hitherto not been mentioned, apart from the few cases where jaundice contributed to the toxic reaction.

The other reactions mentioned in Table 5 are in agreement with those reported by other investigators, but 1 case with neurologic signs must be mentioned separately (the other case was questionable). A brief protocol is as follows:

CASE 2. A woman aged 64 had diabetes, slight hypertension and an adenoma of the thyroid. There were no signs of cardiac failure. She had been ill for 10 years and had often been hospitalized for diabetic coma and her diabetes was very difficult to control. The manifestations of thyrotoxicosis were insignificant and the diagnosis was only made when she was brought to our hospital, at which time she had a basal metabolism rate of +65. Iodine therapy was instituted, but she soon appeared to be iodine-resistant. As we did not know of thiouracil at that time, she was given a series of Roentgen ray exposures with continued iodine therapy. She remained unimproved and at the same time refused subtotal thyroidectomy. Following this, over a period of 4 months, she was given gradually increasing doses of methylthiouracil from 1 to 2.2 gm. a day, with very little effect (as we would now anticipate) except a slight reduction in the basal metabolism rate to +40. The doses were then gradually decreased to 0.8 gm. a day, yet slow improvement continued, and she now began to gain in weight, her diabetes was more

easy to control, and she required less insulin. The patient was continued on 0.8 gm. a day and was thereafter treated as an ambulant patient. It was difficult to persuade her to report regularly, because of difficult transportation during the war, and 75 days after the last control observation, which was satisfactory, she came to the hospital in a serious condition. The first symptom she had complained of at home had been pain and difficulty in control of her left leg. On admission to the hospital, she looked somewhat myxedematous but her basal metabolism rate was only -1. At that time she could not walk at all. Objective examination showed paresis of the quadriceps on the left side but muscular strength was reduced in both legs and in the right arm. The patellar reflex was lost and the plantar reflex was diminished, acting in a peculiar, slow way. The Babinski sign was positive on the left side. There was ill-defined dysesthesia over the left thigh but no definite changes corresponding to the distribution of any peripheral cutaneous nerve. The spinal fluid showed no increase in cells, with albumin 30, and globulin 1. One month after the drug was withdrawn the patient began to walk and later did not have any disturbance of gait or other neurologic signs.

SURVEY OF REPORTS ON METHYLTHIOURACIL. Table 6 gives a survey of the literature on methylthiouracil treatment. There is a surprising difference between the various statements, the 2 largest series by Meulengracht<sup>29</sup> and Frisk<sup>16</sup> show extraordinarily good results. This may be due to some extent in the work of Frisk to his use of small doses and also because he does not give any details in his short summary. The percentage of sustained remissions in the whole material follows rather closely those seen in our cases, but in our patients the relapses were a little more common (20% as compared with 12%). Our figures on partly ineffective treatment are possibly too high, as explained earlier in this article. The number of discontinued treatments because of repeated reactions in our group which received the relatively small doses of methylthiouracil is a little higher (12% as against 7%), but the incidence of mild

TABLE 6.—REVIEW OF PUBLISHED DATA ON METHYLTHIOURACIL TREATMENT—A COMPARISON WITH THE RESULTS OF THIOURACIL

Authors	No. cases	Range of daily drug dose (gm.)		Treatment effective							Treatment discontinued because of reactions				Mild recurrent reactions not interfering with therapy
		Initial period	Maintenance period	Sustained remission after withdrawal	Average follow-up time after withdrawal	Preoperative treatment	Therapy discontinued not because of reaction	Reduction in drug successful, no attempt to withdraw	Remission after withdrawal	B Treatment partly ineffective	All cases	Agranulocytosis	Others		
Magnusson <i>et al.</i>	49	1.2-0.1	0.15-0.02	3	4 mos.	3	1	30	5	1	4	1	3	1	
Mortensen <i>et al.</i>	17	1.8-1.0	0.2	1	5 mos.	0	1	1	1	1	1	1	1	3	
Harsloef	12	1.0-0.8	0.2	1	3 mos.	0	1	1	1	1	1	1	1	4	
Ehlerßen	15	1.0-0.5	0.2	1	1	1	1	1	1	1	1	1	1	1	
Landtack	35	0.8-0.5	0.2	1	1	1	1	1	1	1	1	1	1	1	
Kristiansen	1	1.0	0.2	1	1	1	1	1	1	1	1	1	1	1	
Leschly-Jacobsen	4	0.8-0.6	0.2	1	1	1	1	1	1	1	1	1	1	1	
Vindborg	10	0.8	0.2	1	1	1	1	1	1	1	1	1	1	1	
Thyssen	28	0.8-0.6	0.2	1	1	1	1	1	1	1	1	1	1	1	
Westergaard	22	1.2-1.0	0.03	45	94 mos.	10	1	75	5	4	7	1	7	5	
Meulengracht	114	0.75-0.4	0.01-0.05	17	6 mos.	8	1	70	7	1	3	1	1	5	
Fück	109	0.5-0.4	0.01-0.05	17	6 mos.	8	1	70	7	1	3	1	1	5	
Harrestrup-Andersen	25	0.8	0.2	1	1	10	1	1	1	1	1	1	1	1	
Vagt	17	0.8	0.2	1	1	10	1	1	1	1	1	1	1	1	
Vagt-Lorentsen	12	0.8	0.2	1	1	10	1	1	1	1	1	1	1	1	
Wilson	30	1.0-0.6	0.1-0.025	3	12 mos.	0	1	1	16	2	1	1	1	2	
Lays	10	1.0-0.8	0.1-0.05	1	1	1	1	1	10	2	1	1	1	2	
This author	61	2.2-0.1	0.2-0.05	16	74 mos.	4	2	10	12	4	13	1	12	21	
Total	694	..	..	86	..	71	5	191	45	18	42	9	30	69	
% of total cases	..	..	..	21	..	..	..	..	12	3	7	1.49	..	11	
van Winkle	5745	..	..	..	..	..	..	..	..	4.3%	7.9%	2.50%	..	9%	
Moore	1091	..	..	..	..	..	..	..	..	..	..	1.74%	..	..	

recurrent reactions is much larger than of any other authors.

A comparison of results of methylthiouracil treatment with those in a large series of thiouracil treatment collected by van Winkle *et al.*,<sup>45</sup> and Moore<sup>30</sup> shows about the same rate of partly ineffective treatment, discontinued treatment and agranulocytosis, whereas the mild recurrent reactions are less in the latter. This may be due to the fact that van Winkle's cases are collected from a number of clinics and not seen by the investigator personally.

At present it is impossible to make any comparison of methylthiouracil with propylthiouracil. It can only be pointed out that the effective doses seem to be the same.

**Comment.** It has been proved that methylthiouracil is a powerful antithyroid drug and it seems to exceed thiouracil in strength both in rat experiments and in human therapy. The difference is not great or significant.

A comparison with propylthiouracil is difficult, as the dosages of both drugs have yet to be stabilized, but it is clear that propyl- and methylthiouracil are to be administered in approximately equal doses. The earlier discrepancies between the rat experiments on the goitrogenic effect and the potency of the drugs in man are explained in a natural way by McGinty and by Christensen, and supply the reason for the failure of propylthiouracil to be as effective as would be expected.

Sensitivity to the drugs is even more difficult to compare, but thiouracil and methylthiouracil seem equal when one compares the fairly large series of methylthiouracil treatments collected by the Scandinavian and English investigators with the thiouracil series of Moore and van Winkle.

In our cases there is a high incidence of small but recurrent reactions. The reason for this lies not alone in the greater dosage used, because even in the small dosage group the incidence of reactions is high. Our attitude towards methylthiouracil

was critical from the beginning because of the unphysiologic nature of the therapy and made us very alert and keen to find fault. Moreover, the many positive tests for urobilin constitute a considerable fraction of the so-called reactions. How much the reactions are due to allergy and how much to overdosage, it is impossible to say, but agranulocytosis especially seems to be a fairly late reaction, not caused by overdosage. There can be no doubt, from the common incidence of a positive urobilin test in association with other signs of reaction to methylthiouracil, that this test represents a toxic manifestation. The addition of this simple check-up is therefore advocated.

When using these drugs one has constantly to have in mind all the possible reactions to thiouracil compounds. We are dealing with drugs which cause reactions more often than do the sulfonamides. Moreover, both in the initial period and in maintenance therapy, we are using the drugs for a long period. The danger of agranulocytosis is constant, even if one uses propylthiouracil, following which such reactions have lately been observed by Shibley.<sup>37</sup>

Before radioactive iodine can come into common use, antithyroid drugs are a valuable form of therapy and the goal must be to reduce the dosage of the antithyroid substance as far as possible without diminishing its effectiveness and thus avoid reactions. The work of Danowski, Man and Winkle is very interesting in this direction and ought to be followed up, using methylthiouracil instead of thiourea; but it is quite possible that this procedure will not work in patients who are iodine-resistant, as they seem to constitute a special group.

Not only is it important to choose the correct minimal, initial dose, which we believe should not exceed 0.4 gm. a day, but it is also important to select the patients carefully to avoid unnecessary subtotal thyroidectomy which, even if the technique is perfect, has a mortality as high as 1.6% according to Wijnblad.<sup>41</sup>

The percentage of complications (tetany and paralysis of the recurrent laryngeal nerve) is 2.8 and these figures are much higher when a second subtotal thyroidectomy is necessitated because of relapse (10 to 15%).<sup>7</sup>

From the standpoint of indications, anti-thyroid drugs have an important rôle in the treatment of cases which are: (1) too great a surgical risk or (2) in which operation is refused, or (3) which have had a relapse after a subtotal thyroidectomy. Unfortunately, many elderly patients belong to these 3 groups and as it has been shown, the very best results with methylthiouracil have not been reached in the elderly, as these patients do not have a sustained remission, but must continue on a maintenance dose. Another indication is (4) preoperative treatment. Methylthiouracil, together with iodine, for 10 days prior to operation, seems to lower the risk of a postoperative thyrotoxic crisis. A final (5) indication is constituted by those cases in whom one can expect "cure" from the treatment.

The percentage of "cures" differs greatly: reports<sup>5,6,35,43</sup> range from 20 to 82%, the mean being 54%. The reasons for this are: (1) the rather small material published; and (2) the rather short observation periods (only a few reports have an observation time longer than 9 months). Both in the literature and in our experience there is good evidence that a fairly high number of cases eventually do without therapy and remain well, especially in patients in whom the disease was not of long standing, the goiter comparatively small, and the patient in the younger age group. As Rose has pointed out, this group equals that group which, before the days of antithyroid drugs, one would expect to have had a self-limited course.

There is, on the other hand, no doubt that even the experienced worker has difficulty in predicting what course an individual case will run, and that prolonged iodine and Roentgen ray treatments have often brought the patients into trouble. Methylthiouracil is there-

fore clearly indicated in the above-mentioned cases. The maintenance therapy should not, however, be continued beyond 1 to 1½ years as it seems as if the chance of a sustained remission after this time is rather unlikely. At that time one ought to propose operation which would involve little risk, the patients not having had symptoms for 1 year.

Finally it is important to stress cases in which antithyroid drugs are contra-indicated: (1) large intrathoracic goiter; (2) large adenomatous or diffuse goiter which is rapidly increasing; (3) in non-coöperative patients, where the control is difficult or even impossible; (4) thyrotoxicosis which is due to acromegaly (we have seen such a case which was resistant to methylthiouracil, as have Rose<sup>35</sup> and McGullagh<sup>36</sup>); (5) thyrotoxicosis in pregnancy is an unsettled matter. We have observed 1 case with a normal pregnancy and the birth of a normal child and so has Vogt,<sup>45</sup> but Frisk<sup>16</sup> has seen a child which was born with a pronounced exophthalmus. Freisleben and Kjerulf-Jensen<sup>15</sup> have shown that thiouracil passes the placenta in rats but that the newborn rats are normal. In the lactation period thiouracil is found in the milk and can do great harm to the offspring. The conclusion from this is that thiouracil should be avoided if possible in pregnancy and not used in the lactation period.

**Summary.** 1. In 61 patients with thyrotoxicosis so treated, methylthiouracil has been proved a potent antithyroid drug, but it causes reactions similar to those following thiouracil.

2. In 18 iodine-resistant cases of thyrotoxicosis treated with methylthiouracil, the basal metabolism rate fell much more slowly than is ordinarily the case.

3. Increasing the dosage of methylthiouracil beyond a certain high level is of no value.

4. To 18 patients large doses of methylthiouracil were given. The average dose was 1.2 gm. daily and the drug had to be discontinued in 8 cases (44%) and caused reactions in 14 patients (78%). A smaller

average dose of 0.57 gm. was given to 43 patients and in these patients the drug had to be discontinued in 5 cases (12%) and caused reactions in 20 cases (47%). In this group of patients there occurred a case of agranulocytosis which recovered.

5. The largest single dose recommended is 0.4 gm. a day, and even if this does not give any results for the first 7 or 8 weeks it is justifiable to wait 2 or 3 weeks more for a fall in basal metabolism rate.

6. Of 61 patients with thyrotoxicosis it was possible to carry the treatment through in 44 patients and they were fully capable of work in an average of 1.2 months after therapy was started.

7. Sustained remission with an average observation period of  $7\frac{1}{2}$  months occurred in 16 patients (26.2%) after a treatment of approximately 5 months' duration.

8. The sustained remissions occurred most frequently in cases with a small to moderate-sized goiter, in the young or

middle-aged groups, especially in men, and in cases where the disease had not been of long standing. The complications and the severity seemed to have no significant influence on the ultimate result of therapy.

9. In 4 cases of thyrotoxicosis, methylthiouracil treatment, even for a long period, was unsuccessful.

10. Among reactions to methylthiouracil a positive test for urobilin in the urine is shown to be common and important.

11. A survey of the literature on methylthiouracil has been made and the results are compared with those of thiouracil and propylthiouracil. Methylthiouracil seems more effective than thiouracil and about as effective as propylthiouracil.

12. Indications for therapy with anti-thyroid drugs are outlined.

13. Methylthiouracil is of no use in elevated basal metabolism rate caused by acromegaly.

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# THE EFFECT OF LUMBODORSAL SPLANCHNICECTOMY ON THE BLOOD VOLUME AND "THIOCYANATE SPACE" OF PATIENTS WITH ESSENTIAL HYPERTENSION

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THIS investigation was undertaken as part of a comprehensive study of the effects of sympathectomy on the hemodynamic functions of patients with essential hypertension. It was considered worthwhile to rule out the possibility that the reduction in blood pressure is accompanied by significant alterations of total blood volume, and, incidentally, to obtain information on the effects of the operation on the intravascular and extracellular fluid compartments of the body.

Following sympathectomy in normal cats the plasma volume increased,<sup>11</sup> whereas, in dogs with experimental renal hypertension sympathectomy produced either no change<sup>4</sup> or a decrease in red cell volume.<sup>16</sup> The present report presents the results of blood volume and "available fluid" ("thiocyanate space") studies in patients with essential hypertension before and after lumbodorsal splanchnicectomy.

**MATERIALS AND METHODS.** The subjects were a heterogeneous group of 10 patients with essential hypertension. The measurements of plasma volume using the dye T-1824, and of "available fluid" volume using a 5% solution of sodium thiocyanate intravenously were determined before operation and at various intervals after operation.

The method of Gregersen and Stewart<sup>6</sup> for the simultaneous determination of blood volume and "thiocyanate space" was modified for use with the Coleman junior spectrophotometer. The blood samples were collected in 4 cc. hematocrit tubes containing a measured amount of liquid

oxalate mixture in isotonic saline as described by Emerson and Ebert.<sup>2</sup>

The plasma specific gravity of each sample was determined with the Barbour and Hamilton falling drop apparatus and the dyed plasma samples were corrected for fluid shifts as recommended by Gregersen.<sup>7</sup> After such correction straight line dye concentration curves were obtained on a semi-log plot (logarithm of the plasma dye concentration plotted against time). Using this method uniform rates of dye disappearance (approximately 5% in the 1st hour) were obtained, thus confirming the observations of Noble and Gregersen.<sup>14</sup> For this reason and because of the greater convenience we determined the plasma volume from the 10 minute sample in the latter half of this investigation.

Since in some individuals thiocyanate reaches an equilibrium with the extracellular fluid slowly, and because there is no appreciable change in concentration from the 1st to the 4th hour following injection,<sup>1</sup> the plasma samples used to calculate the "available fluid" volume were drawn 1½ to 2 hours following injection. In view of the lack of adequate information concerning the precise volume distribution of thiocyanate "correction" factors were not used. The "available fluid" volume as used in this study expresses the total volume in which thiocyanate is distributed, including the plasma volume, the amount that enters the red cell, and its distribution in the extracellular space.

TABLE 1.—BLOOD VOLUME AND AVAILABLE (THIOCYANATE) FLUID CHANGES FOLLOWING LUMBODORSAL SPLANCHNICECTOMY.

Patient	Sex	Age	Time	Height (cm.)	Weight (kilo)	Blood pressure (mm. Hg)	Plasma volume (cc.)	Hematocrit (%)	Total blood volume (cc.)	Change (%)	"Available fluid" (cc.)	Change (%)
J. F.	M	25	Preoperative	175	80	155/100	2,800	50.5	5,720	..	20,500	0
			P 1st stage 10 days		77	170/135	3110	45.0	5,650	-1	20,600	+23
			P 2nd stage 12 days		76	135/95	2930	47.5	5,610	-2	24,100	+10
			3 months postoperative		78	120/85	2780	43.0	4,880	-14	21,600	+9
			6 months postoperative		83	145/100	2930	47.5	5,610	-1.5	21,250	+16
			Preoperative	162	39	225/150	1575	40.5	2,350	...	11,900	+13
E. L.	F	21	P 1st stage 8 days		39	170/100	1880	33.0	2,950	+11	13,900	+16
			P 2nd stage 10 days		38	200/110	1680	39.0	2,750	+5	13,100	+13
			3 months postoperative		40	115/88	2000	40.1	3,350	+25	12,700	+8
			6 months postoperative		38	145/125	...	33.0	...	..	12,000	0
			Preoperative	176	77	165/135	3240	45.5	5,950	..	20,200	+16
			P 2nd stage 12 days		72	170/120	3000	37.5	4,900	-16	21,800	-10
J. M.	M	42	3 months postoperative		68	115/88	2900	42.5	5,050	-10	18,200	-3
			6 months postoperative		77	135/95	3350	43.1	5,900	-1	19,600	+28
			Preoperative	170	74	165/110	2760	45.5	5,070	+5	18,000	-9
			P 2nd stage 8 days		70	130/90	3230	33.5	5,140	-2	16,400	0
			3 months postoperative		72	145/100	3100	33.0	5,000	-1	18,000	+2
			6 months postoperative		72	130/100	2,400	42.7	4,950	-10	19,500	+18
R. D.	M	27	Preoperative	181	64	220/140	3420	40.8	5,970	-6	21,800	+6
			P 1st stage 5 days		63	220/155	3250	37.0	5,170	+4	20,400	+6
			Immediate P 2nd stage		..	160/130	3370	33.0	5,430	-9	18,200	+13
			P 2nd stage 12 days		62	185/140	3370	37.0	5,800	-3	14,300	-3
			6 months postoperative		65	195/155	3320	43.5	6,230	-5	14,700	+3
			Preoperative	177	77	190/135	2360	41.0	5,125	-6	20,115	+24
W. R.	M	33	P 2nd stage 10 days		72	160/140	2220	51.0	4,525	-9	19,200	+13
			Preoperative	151	57	208/105	2300	40.0	3,400	-3	13,500	-3
			P 1st stage 5 days		57	140/86	2320	32.5	3,740	-3	14,300	+3
			P 1st stage 10 days		57	160/95	2310	37.0	3,375	-6	14,700	+24
			P 2nd stage 15 days		57	165/110	2200	39.0	3,320	-9	19,200	+13
			Preoperative	178	86	160/120	2,400	43.8	5,510	-9	24,300	+15
J. V.	M	35	P 2nd stage 5 days		84	155/110	2760	44.5	4,975	-4	19,700	+22
			2 months postoperative		85	135/112		47.5		..	22,600	+22
			Preoperative	170	80	165/110	3210	44.7	5,500	-4	21,730	+22
			P 1st stage 10 days		77	210/110	3150	43.5	5,570	-14	21,730	+22
			P 2nd stage 20 days		73	140/96	3090	40.2	5,000	-14	21,730	+22
			Preoperative	175	65	210/130	2350	53.0	5,120	-5	19,700	+22
J. W.	M	45	P 2nd stage 10 days		65	170/110	2370	50.5	5,170	-5	19,700	+22
			Preoperative							..	22,600	+22
			P 1st stage 10 days		77	210/110	3150	43.5	5,570	-4	21,730	+22
			P 2nd stage 20 days		73	140/96	3090	40.2	5,000	-14	21,730	+22
			Preoperative	175	65	210/130	2350	53.0	5,120	-5	19,700	+22
			P 2nd stage 10 days		65	170/110	2370	50.5	5,170	-5	19,700	+22

RESULTS. The results listed in Table 1 and Figures 1 and 2 reveal a decrease in total blood volume of from 1 to 16% in 9 of the 10 subjects during the convalescent postoperative period. In most cases

this was due to a decrease in red cell volume as manifested by a fall in hematocrit. These observations were made about 10 days postoperatively in order that the results would not be confused by the

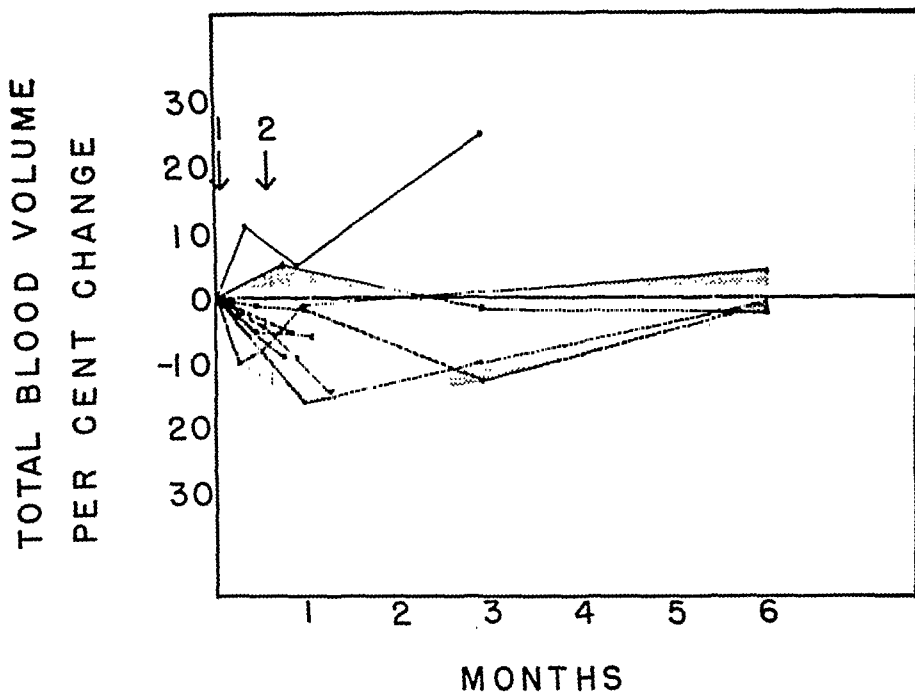


FIG. 1.—Per cent changes in total blood volume following lumbodorsal splanchnicectomy. The shaded area contains the values found in 9 of the 10 subjects studied. The arrows indicate the times of operation.

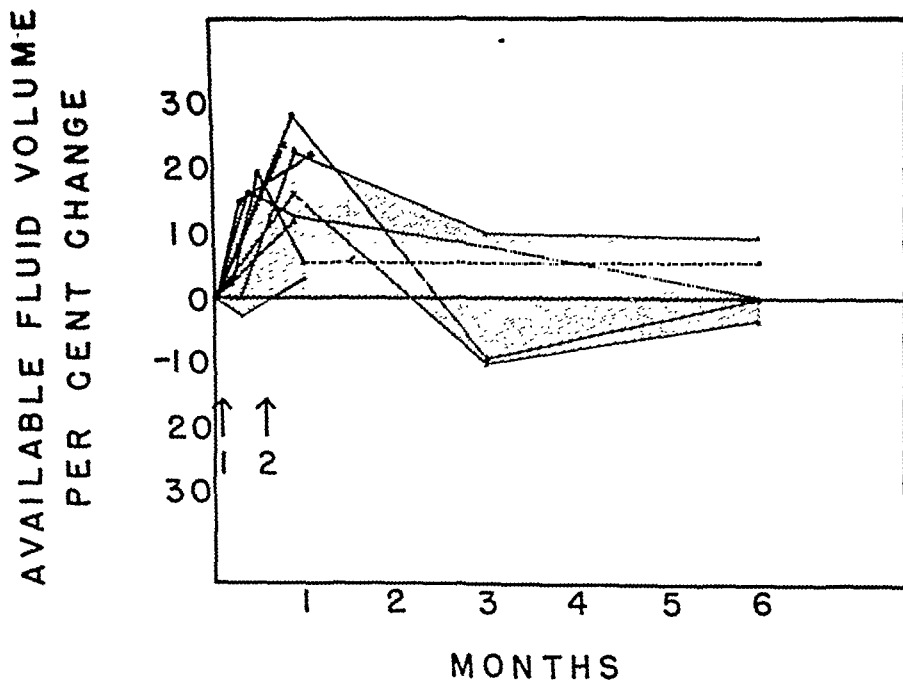


FIG. 2.—Per cent changes in "available fluid" volume following lumbodorsal splanchnicectomy. The shaded area contains the values found in the 9 subjects studied. The arrows indicate the times of operation.

routine administration of blood and other parenteral fluids during the operative and immediate postoperative periods.

Coincident with the fall in total blood volume there was an increase in "available fluid" in all of the 9 cases studied varying from 3 to 28%. In all of the 5 patients followed for 6 months the total blood volume and "thiocyanate space" was restored to approximately the preoperative levels at the end of the period of observation. In 4 of these, however, the hematocrit remained slightly below the preoperative value, the deficiency being made up by a slight increase in plasma volume.

The decrease in total blood volume in the postoperative period has no relationship to changes in arterial pressure. Patients with slight or no fall in blood pressure exhibited the same decrease in total blood volume as those who had significant reductions in blood pressure. Thus, patient R. D. whose blood pressure preoperatively was 220/140 and 5 days postoperatively was 220/155 revealed a decrease in total blood volume of 10%. Patient J. S. whose blood pressure fell significantly from 208/105 preoperatively to 160/95 10 days postoperatively also exhibited a decrease in total blood volume of 5%.

Similarly, at the end of 6 months there was no correlation between changes in arterial pressure and changes in total blood volume. For example, the total blood volume had returned to within 2% of the preoperative value in both patient J. F. whose blood pressure was essentially unchanged and patient J. Mc. who exhibited a definite fall in arterial pressure from 165/135 to 135/95.

**Discussion.** The purpose of this investigation was to determine whether or not significant changes in blood volume and "available fluid" volume were produced following partial sympathectomy. Long-term observation of 5 patients revealed that at the end of 6 months following operation significant changes had not occurred, despite the fact that in the majority of these cases the blood pressure was

significantly lower than the preoperative value.

However, during the course of the study definite trends in blood and available fluid volume were noted in the period from 8 days to 2 weeks after operation. These changes, which consisted of a reduction in red cell volume and an increase in "available fluid" volume, have been observed following other types of major surgery.<sup>13</sup> The fluctuations observed, therefore, cannot be considered to be a specific consequence of sympathectomy. Indeed, an increase in "thiocyanate space" has been observed in other conditions, such as lobar pneumonia<sup>14</sup> and infectious hepatitis,<sup>12</sup> as well as after surgical operations, and may represent simply a non-specific reaction of the body to injury.<sup>17</sup>

The failure of the hematocrit value to return to the preoperative level over a period of 6 months following operation is of interest. In dogs with experimentally induced polycythemia Schafer<sup>16</sup> has observed a definite reduction in red blood count following sympathectomy. He also noted a fall in hematocrit in a patient with polycythemia rubra vera who had undergone sympathectomy. Green<sup>5</sup> has reported a marked reduction in the hematocrit value following surgical excision of a pheochromocytoma in a patient who had chronic hypertension.

These observations suggest a relationship between the sympathetic nervous system and the red blood cell volume. However, the change may be more apparent than real, as it is possible that sympathectomy, by altering the caliber of the smaller vessels, may cause a redistribution of the red cell mass in the vascular system. This in turn would change the cell-plasma ratio in the larger vessels from which sampling is accomplished.<sup>3,8,19</sup>

On the basis of surface area the preoperative total blood volume values were within the normal range as defined by Gibson and Evans.<sup>9</sup> This is in agreement with the conclusion of Harris and Gibson<sup>10</sup> that the blood volume is normal in essential hypertension. The values for "avail-

able fluid" volume similarly fell within the normal range when compared on the basis of surface area.<sup>18</sup>

**Summary and Conclusions.** 1. Repeated blood and "available fluid" determinations were made on a series of 10 cases of essential hypertension for periods up to 6 months following lumbodorsal splanchnicectomy.

2. The total blood volume was reduced in 9 cases in the period from 8 days to 2 weeks following operation, due primarily to a diminution in red cell volume. Despite a continued reduction of blood pressure the total blood volume was restored to the approximate preoperative level at the end of 6 months following operation. A slight reduction of the hematocrit value persisted, the deficiency being made up by a

compensatory increase in plasma volume.

3. Coincident with the reduction in blood volume noted in the 2nd postoperative week there was an increase in "available fluid" volume. This elevated value was restored to the preoperative level over a period of several months.

4. Previous observations that the total blood volume is within normal limits in patients with essential hypertension were confirmed.

5. In relation to surface area the "available fluid" volume of hypertensive subjects was also found to be within the normal range.

6. The reduction in blood pressure following sympathectomy is not dependent upon changes in total blood or "available fluid" volume.

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# FLUORESCEIN STUDIES IN PERIPHERAL VASCULAR DISORDERS

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ALTHOUGH there is a number of procedures which are now employed to determine the status of the peripheral circulation, any method which may add to our knowledge or promise more information is desirable. Contributions and reports on "circulation time" which indicated blood flow seemed to offer some encouragement. These studies were based on arm to tongue and arm to lung time, whereby one could identify whether the right heart or the left heart was involved or which one was predominating.

More recently fluorescein was used in determining circulation time. It was given intravenously and investigators claimed that this method was an improvement over the other substances because it eliminated personal equation of the patient, and the end point could readily be seen by the observer by the appearance of the dye upon the lips or the conjunctiva.<sup>2,4</sup> Furthermore, fluorescein was particularly preferable when the patient could not cooperate by calling the end point for the circulation time.

On a previous occasion, one of us attempted to investigate the circulation time in the extremities, both upper and lower. A 20% solution of calcium gluconate was used. The results at that time were vague and unsatisfactory, and our series was not extensive enough to warrant publication. Our conclusions concurred with those of Berk<sup>1</sup> who used magnesium sulfate. His results were likewise unsatisfactory because of the large percentage of "blanks"; that is, where no sensation of warmth was felt in the peripheral parts. He noted that "two-thirds of all the individuals showed blanks at some time or other."

Our hopes were encouraged when Lange<sup>4,5</sup> published his results of fluorescein in a patient with embolic occlusion and one of diabetic gangrene. We considered that fluorescein, with its advantages over other substances commonly employed for circulation time, offered more favorable results.

**Method of Study—Technique.** After the patient has rested for about 15 to 20 minutes, he is placed on a table in the recumbent position. The limbs are exposed and inspected preliminarily with an ultraviolet bulb covered with a purple glass filter. This is to search for any abnormalities and to acquaint oneself with the color and condition of the extremities.

Under the usual sterile precautions an 18 gauge needle is inserted into the ante-cubital vein.

The room is then darkened and 4 cc. of fluorescein solution (20%)\* is rapidly injected (3 cc. was used at first but later 4 cc. of the solution was used in the remaining cases).

The examiner, with stop-watch in hand, observed the lips which are the first to show the end point of the distribution of the dye. A greenish or greenish-yellow color can clearly be seen. Then the hands and lower extremities are carefully scrutinized and the time required for the distribution of the dye to these parts is recorded. In our study we charted (1) the elbow to lip time, (2) elbow to hand time and (3) elbow to foot time.

**Selection of Cases.** A series of 89 patients were studied, 69 of which were analyzed for statistical purposes. Forty-five patients had some form of vascular disorder ranging from arteriosclerosis obliterans, thrombo-angiitis obliterans and embolic occlusion to Raynaud's syndrome, chronic

\* Fluorescein supplied by courtesy of Eli Lilly & Co., Indianapolis, Indiana.

leg ulcers and vasospastic disorders. They were taken consecutively from the vascular clinic.

Another series of 24 patients were similarly studied; they were obtained from the medical and surgical wards. Some were convalescing from operations or were admitted for study. The medical cases included cardiac and miscellaneous conditions. However, these cases were presumably not suffering from any peripheral vascular disorder. They were of various ages, color and sex.

TABLE 1—APPEARANCE TIME

*Peripheral Vascular Disease Group*

	Times (sec.)	Average (sec.)
Arm to lips . . .	12-30	16.0
Arm to hand . . .	15-51	31.2
Arm to foot . . .	30-120	61.4

*Non-vascular Disease Group*

	Times (sec.)	Average (sec.)
Arm to lips . . .	7-25	14.4
Arm to hand . . .	17-60	28.5
Arm to foot . . .	26-60	53.4

**Results and Discussion.** Table 1 shows the appearance time of the fluorescein on lips, hands and feet in the vascular group and those patients who presumably were not suffering from peripheral vascular disorders.

*Arm to Lip Times.* Twenty-two of the combined group showed an appearance time from 8 to 13 seconds, while 47 revealed a circulation time ranging from 14 to 25 seconds. These results seem to compare satisfactorily with Lange's figures.<sup>6</sup> He noted that in studying 89 normal adults above the age of 20 years, the appearance time at the lips was between 15 to 20 seconds, an average of 17.1. Fishback's<sup>2</sup> figures were from 15.6 to 17 seconds; he gave no average in his series. Our average was 14.4 to 16 seconds.

*Arm to Hand Time.* Thirty-four cases showed an appearance time between 17 and 28 seconds (49.3%); 17 of the combined group revealed the dye between 29 and 35 seconds (24.6%). Collectively 51 of the patients studied (74%) showed the dye in the hands between 17 and 35 sec-

onds. Our average for the non-vascular cases was 28.5 seconds and 31.2 seconds for the peripheral vascular group.

These figures have been arranged in Table 2 showing the comparison with those obtained by Berk,<sup>1</sup> whose averages were 19.2 seconds for normals and 25.1 seconds for the vascular disease group.

TABLE 2—ARM TO HAND TIME

*Fluorescein*

	Appearance time (sec.)	Average (sec.)
Non-vascular . . .	17-60	28.5
Vascular . . . . .	15-51	31.2

*Magnesium Sulfate (Berk)*

	End point (sec.)	Average (sec.)
Non-vascular . . .	6-61	19.2
Vascular . . . . .	12-60	25.1

Table 2 shows the comparative results of the arm to hand time using fluorescein and magnesium sulfate. Twelve of the patients revealed a prolonged time between 41 to 60 seconds, 10 being in the vascular series and 2 in the non-vascular. He believes that the delayed appearance of the dye could be explained on the basis of age and cardiac disease. However, some of them might have had a variable degree of interference with the circulation as well.

*Arm to Foot Time.* Almost invariably the appearance of fluorescein was delayed in the lower extremities. It was first seen on the lips, then on the hands, and last on the feet. Only in 2 or 3 cases did the dye appear in the feet as promptly as it was seen in the hands. Its late appearance in the feet is quite understandable when we take into consideration that the skin temperatures are always lower in the feet than in the upper extremities. It is also an accepted fact that the vasoconstrictor gradient is greatest in the feet. It may be noted that 6 cases in the non-vascular group (25%) showed the dye between 30 to 40 seconds in comparison with 6 cases in the vascular group (17.8%); 11 cases of the non-vascular series (46%) showed an appearance time between 30 to 50 seconds compared with 15 cases of the vascular series (33%). The analysis of the



arm to foot time in these cases was carried out to a 3 minute period. It was noted in the cases that showed a markedly delayed appearance time over 50 seconds, that this occurred in 43.5% of the vascular cases as compared with 18.2% of the non-vascular cases or about 2.5 to 1. These facts we believe are significant and indicate that vascular disorders can be responsible for the prolonged appearance time. The delayed end point of the fluorescein in our series of the vascular group was probably due to the disturbance in the circulatory system. However, a few of these patients may have had some cardiac condition as well but we are reasonably certain that the age element was eliminated.

*Untoward Effects.* Our experience compares with other investigators who used fluorescein in their studies. There were no definite reactions. Two of our patients vomited shortly after the test but this, we feel, was due more to nervousness and apprehension than to the effect of the dye. Over 100 injections were given in our studies. The dye was rapidly eliminated by the kidneys. The patients were told to expect a greenish tinge on the skin to remain for a few hours and that the urine would be discolored temporarily.

*Normals.* We realize that before any definite conclusions can be reached in reference to the employment of fluorescein for investigating the peripheral circulation, one must have a fairly acceptable normal appearance time. Because of the scarcity of investigations with this substance, we were handicapped in determining what the normal standard is. For the benefit of other investigators in the future we would suggest the following figures. These are based on our observations with corrections which we suggest that would make them approximate of what may presumably be normal. This will particularly apply to the arm to foot time which will

be more than the other regions.

These figures are higher than those quoted by Berk in his studies of the circulation time in the lower extremities using magnesium sulfate. In his normal group he noted that the end point ranged anywhere from 7.4 to 8.2 seconds to 50.1 to 56.2 seconds, an average of 24.1 seconds. In the pathologic series, he recorded 18 to 70 to 75 seconds, averaging 35.7 to 36.1 seconds. His figures are quite at variance with those suggested by our studies. However, we feel that it is impossible to arrange any standard figures for those patients with peripheral vascular disease.

However, there is another fact which deserves some comment at this time and which may suggest an earlier normal appearance time than the figures quoted by us. Lange<sup>5</sup> employed fluorescein in 4 patients who had ulcers on the lower extremities. He specified that these ulcers were not arteriosclerotic in type and we presume that the patients were not cardiacs. Fluorescein was seen in the ulcer areas within 23 seconds.

Neller and Schmidt<sup>8</sup> employed fluorescein by making a series of superficial scratches at 2 inch intervals down the legs and observing the appearance of the dye in these areas as a means of determining the level of vascular impairment. However, they do not quote any normal values of appearance time.

Whether the dye may be seen more promptly in an ulcer area than working its way through the peripheral arterioles and capillaries is a matter which we are not prepared to settle at this time.

It may be of interest at this point to comment on some features which are demonstrated by the dye technique. In 1 patient we were impressed with appearance of "blackened-out" areas which on physical examination were rose-colored. These so-called rose spots were described in a previous publication<sup>3</sup> as evidence of early pathologic damages in the smaller vessels. While we were unable to prove this fact by histologic section we are now convinced that these "blackened out" areas

TABLE 3. NORMAL FLUORESCIN APPEARANCE TIME

Arm to lip time . . . .	12-16 seconds
Arm to hand time . . . .	18-28 seconds
Arm to foot time . . . .	40-50 seconds

are due to interference with the circulation. This is in accordance with Lange's views. A second feature was the application of fluorescein in studying the condition of ulcers when skin grafting is considered. Lange<sup>7</sup> pointed out that he was able to select those ulcers with healthy granulations and those which showed definite evidence of interference with blood supply by the use of fluorescein, this distinction not being apparent on ordinary inspection. A third feature which interested us when examining a patient who had a unilateral lumbar ganglionectomy: the appearance time was practically the same in each foot, but the dye was more dense on that side which was operated upon despite the fact that it had a greater degree of involvement. Feature No. 4 was apparent in a patient who had an arteriovenous fistula in the groin. After 3 attempts to obliterate this condition, the patient still had considerable pain and the foot was cold and discolored. On examination with fluorescein the foot and ankle areas were practically "blackened-out" indicating extensive interference with the arterial blood supply.

**Summary and Conclusions.** Eighty-nine patients were studied with fluorescein for the appearance time at the lips, hands and feet. Sixty-five of this series had some form of vascular disease, 24 cases were presumably not vascular. They were various ages and sex.

The appearance time in the lips in the non-vascular group was 14.4 seconds and 16 seconds for the patients with vascular disorders.

The arm to hand time showed an average of 28.5 seconds for the non-vascular

cases and 31.2 seconds for the vascular group.

The arm to foot time ranged from 30 seconds to 3 minutes. However, most of the cases showed an appearance time within 60 seconds, the average for the non-vascular group was 53.4 seconds and 61.4 for the vascular cases. When the appearance time was beyond 60 seconds, the vascular series predominated over the non-vascular about 2.5 to 1.

Other features which may explain a delayed appearance time are old age and cardiac disease. The appearance time is not so easily recognized in the lower extremities and in the colored.

The following figures are suggested for the normal appearance time: arm to lip, 12 to 16 seconds; arm to hand, 18 to 28 seconds; arm to foot, 26 to 60 seconds (average 53.4).

The fluorescein test is superior to other substances which depend on subjective sensations for the end point. The end point with this method is readily recognized. The fluorescein test is harmless and non-toxic, the dye is readily eliminated by the kidneys.

Despite the unavailability of a more definite normal standard for arm to foot time, we were impressed with the delay in appearance time in the lower extremities among patients with known vascular disorders. From this, we infer that it gives information relative to the status of the peripheral circulation. It is helpful in deciding and selecting the proper type of ulcer for grafting. It may be of assistance in determining the level for amputation, but we have had no personal experience with fluorescein along these lines.

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## THE ANTIDIURETIC EFFECT OF MORPHINE AND DEMEROL IN CONGESTIVE HEART FAILURE\*

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ANTIDIURETIC action of morphine has been studied in animals since 1887.<sup>27,30,36</sup> Frey,<sup>18,19</sup> in 1907, concluded that narcosis with morphine hinders the development of a water diuresis. During the next 20 years studies on the water diuresis in animals<sup>16,17,21,32,34,35</sup> continued to confirm this fact. Bonsmann<sup>3,4</sup> and others,<sup>15,33</sup> doing a more careful control than previous workers on the initial state of hydration of the animals, reemphasized the antidiuretic effect of morphine. De Bodo and co-workers, working from 1940 to 1945,<sup>11,12,13</sup> have presented detailed pharmacologic studies made in animals that clearly demonstrate the antidiuretic action of morphine.

The antidiuretic action of various hypnotics has been studied but the results are controversial.<sup>7,24,26,28</sup> Recently de Bodo has shown in animals<sup>13</sup> that some barbiturates have an antidiuretic action.

The effect of drugs on mercurial diuresis has also been studied in animals. This work includes studies of the antidiuretic action of barbiturates,<sup>5,38</sup> chloralose,<sup>5</sup> pituitrin<sup>37</sup> and antipyretics.<sup>1</sup>

In summary, the experimental work in animals has shown that morphine inhibits water diuresis. Whether hypnotics exert a similar effect on water diuresis is controversial. Hypnotics, antipyretics and pituitrin have been shown to exert an antidiuretic effect on mercurial diuresis. This present study concerns itself with the action of morphine on mercurial diuresis.

In man the antidiuretic effect of mor-

phine and allied compounds has long been a clinical impression. It was probably first mentioned in the literature in 1839 when Bouchardat<sup>6</sup> reported the alleviation of the symptoms of diabetes by gradually increasing doses of opium. The report of decreasing urinary volume in diabetes mellitus and diabetes insipidus following morphine has been repeatedly reported since then. Recently, Master has reported as his clinical impression that morphine reduces the effect of mercurial diuretics.<sup>25</sup> The study by Fee<sup>16</sup> using himself as the subject on the inhibition of water diuresis by morphine constituted the first controlled clinical investigation. The clinical studies presented by Hopmann,<sup>23</sup> however, yielded irregular results. His patients were in various stages of digitalization, were not studied under standardized conditions, and were victims of additional diseases such as cirrhosis and nephritis. He stressed morphine as a diuretic. In those instances where it failed to act as such, he explains this failure to initiate diuresis by stating that oral morphine given at night produces diuresis and morphine given during the day does not. Bahn, Iserbeck and Lindemann,<sup>2</sup> on the other hand, presented a controlled clinical series of observations and noted definite decrease in water diuresis following morphine. However, the work of Hopmann served to impress certain workers to such an extent that as late as 1940 a review of recent advances in therapy<sup>8</sup> carried the statement that morphine alone may cause massive diuresis

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in cardiac patients, although it is accepted as an antidiuretic in normal individuals.

Although it might be anticipated from the literature<sup>7,12,17,18</sup> that morphine and demerol would exert no consistent antidiuretic effect on saline diuresis, the frequent use of mercurial diuretics and these drugs during the treatment of cardiac failure makes the study of their interaction a matter of some importance.

**Method.** The study was divided into 2 parts: the action of morphine on diuresis in patients with congestive heart failure, and in normal persons. In patients with heart disease the diuresis was initiated as a result of mercupurin. The study in normal persons was made during water diuresis. All patients studied were in the fasting state. The urine samples were obtained by means of a catheter. The bladder was first emptied and the sample discarded. A preliminary determination of the rate of urinary flow was made during the next 20 minute period, by measuring the volume excreted in these 20 minutes and expressing the urinary flow as cc. per minute. This sample of urine was saved for an analysis of chloride content. Subsequent samples were collected every 20 minutes. In both groups studied, the urine flow during the initial control period remained under 1 cc. per minute. When the urine flow rose above 1 to 1.5 cc. per minute, diuresis was considered to be initiated. The following technique was used to insure complete emptying of the bladder at the end of each 20 minute interval: Pressure over the pubis caused the expelling of the larger proportion of the urine. Twenty to 40 cc. of air was then instilled into the bladder by means of a syringe. If any urine remained, when pubic pressure was again instituted, the urine was expelled ahead of the air, which followed as bubbles. If the bladder was empty the air alone was expelled at once, and with a characteristic explosive sound. This end point was sought at least twice at the end of each period. The concentration of chloride in the urine (expressed as milliequivalents per liter) was measured in each sample by the method of Schales and Schales.<sup>31</sup> The rate of chloride excretion (milliequivalents per minute) was calculated from the urine flow (cc. per minute)

and the chloride concentration (milliequivalents per liter).

**STUDY OF THE ANTIDIURETIC ACTION OF MORPHINE AND DEMEROL IN CARDIACS.** All subjects studied were patients who remained in congestive heart failure despite complete bed rest and full digitalization. All patients suffered from the type of cardiac decompensation in which frequent mercupurin injections were needed to mobilize edema. Each patient received 3 gm. of ammonium chloride daily and a low fluid, salt-poor diet. As soon as daily weights were stabilized on bed rest, mercupurin was given in each case in order to initiate diuresis. In order to establish the type of response obtained with mercupurin alone, control diuretic curves were obtained on a group of 6 patients, each of whom received 2 cc. of mercupurin intravenously. Nine observations were made on these 6 patients. One patient was studied 3 times, 1 patient twice, and 4 patients were each studied once. Nine patients were then studied to determine the effect of morphine on mercurial diuresis. Two cc. of mercupurin were given intravenously and when diuresis was well established the patient received 0.01 gm. of morphine sulfate intramuscularly—usually about 80 minutes after the injection of mercupurin. The urine flow was followed for 3 to 5 hours after mercupurin. The patient was then allowed to reaccumulate edema to the original weight level, and 2 cc. of mercupurin alone were given. Thus, a control diuretic curve with which to compare the curve under the influence of morphine was obtained on each patient.

**STUDY OF THE ANTIDIURETIC ACTION OF MORPHINE IN NORMALS.** Water diuresis studies were made on 4 patients on the wards of Bellevue Hospital. They were all awaiting discharge. Two were convalescing from upper respiratory infections (la grippe, bronchitis) and 2 were victims of mild nervous system disease. All 4 were free of circulatory, renal or hepatic disease. In accordance with De Bodo's technique in animal studies, the 4 patients were completely hydrated before the ob-

servations were begun. This was accomplished by the administration, in the fasting state, of 1000 cc. of water by mouth at 7 A.M. of the day of the study. This water of hydration was excreted in varying amounts over the next 3 hours, depending on the original state of hydration of each subject. Three hours after the first ingestion of water, at 10 A.M., the study was begun. Urine samples were obtained every 20 minutes for  $2\frac{1}{2}$  to 3 hours by the same catheter technique as above. It is known that if a person is completely hydrated, he will excrete almost quantitatively a 1000 cc. of water in 2 to 3 hours. The 4 patients studied demonstrated this clearly in the control observations to which each was subjected. Three of the patients received the second dose of fluid as 1000 cc. of 5% glucose in distilled water, intravenously, given in 45, 40 and 17 minutes respectively. One patient received the second 1000 cc. of water by mouth, given in 5 minutes.

**Results. Cardiac Patients.** The control diuretic curves obtained show in general an early rise in urine flow during the first 3 to 5 hours following the injection of mercupurin. From a normal level of under 1 cc. per minute, the urine flow rose to a minimum level of 2.4 cc. per minute in 1 patient to a maximum level of 10 to 12 cc. per minute in others. The peak of the curve was reached during the first 1 to 2 hours and then the diuretic curve leveled off and was maintained fairly constantly at a plateau range for the next 2 to 3 hours. Chloride concentrations, and therefore chloride excretion rates, behaved in the same manner. In a patient with several diuretic curves, the chloride concentration rose to almost exactly the same level on each trial and remained at this level with a variation of only 10 to 15 milliequivalents per liter.

Nine patients in congestive heart failure were studied to note any effects by morphine on the diuretic curve. In 3 patients morphine was found to have an antidiuretic effect. The latter was interpreted on the basis of a persistent depression of

the diuretic curve obtained during the period of observation and in each patient compared with his own control diuretic curve.

It should be emphasized that in the same patient at the same weight level the diuretic curve follows the same pattern on repeated diuretic trials and the control curves do not show a fall in rate of urine flow during the first 3 to 4 hours.

The first patient (C. P.) was studied repeatedly. In 2 separate observations, each with 1 or 2 control curves, morphine, when administered after the diuresis was in progress, caused a definite suppression of this diuresis (Figs. 1 and 2). This was first noted 40 minutes after the administration of the drug and persisted for as long as  $2\frac{1}{2}$  hours. The urine flow fell from 10.3 cc. and 7.4 cc. per minute to 2.35 cc. and 3.7 cc. per minute respectively, and then gradually rose to 7.75 cc. and 5.8 cc. per minute at the end of the period of study. In a third observation, when morphine was given 10 minutes before mercupurin, *i. e.*, before the diuresis developed, the diuretic curve was flattened and ranged between 1.47 and 5.14 cc. per minute and had not risen to the control level, 8.5 cc. per minute, 4 hours after morphine was given (Fig. 3). As an additional control in this patient, a sterile water injection was given intramuscularly after the development of the diuretic state but the diuretic curve was unaffected (Fig. 2). The intramuscular injection of 75 mg. of demerol after the diuresis had started produced in this same patient the same antidiuretic effect as morphine and caused a slight decrease in urine chloride concentration (Fig. 4). However, the effect was noted sooner (24 minutes after demerol was given). The chloride concentration in the urine differed very little from the control levels during the antidiuretic effect of both these drugs. Therefore, the chloride excretion rate varied only with water output or urine flow. The total chloride excretion during the period studied was markedly reduced under the influence of morphine and

demerol as compared with the control periods. Control total chloride excretion over 4 hours ranged between 219 and 314 milliequivalents and during antidiuresis fell to a range between 103 and 171 milliequivalents (see Table 1).

The second patient (S. W.) was also studied repeatedly. An antidiuretic effect was also noted with morphine in 2 separate

studies and once with demerol. The urine flow rose to 2.1 cc. and 2.09 cc. per minute and under the influence of the drugs fell to 0.24 cc. and 0.95 cc. per minute. In addition, renal plasma flow as determined by the para-amino-hippuric acid clearance test<sup>22</sup> was studied during 1 series of observations. This renal plasma flow showed no variation from the normal figure

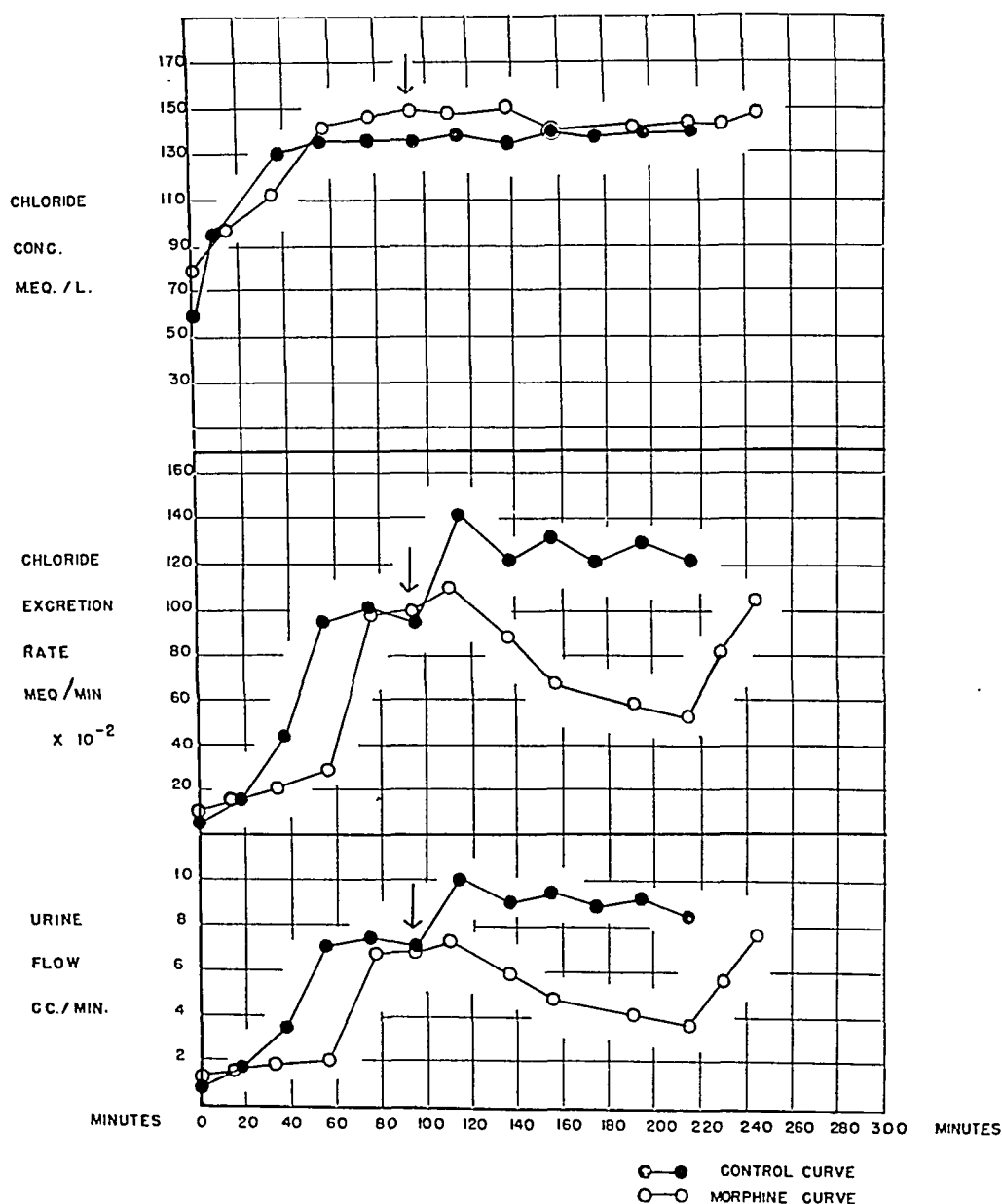


FIG. 1.—*The Antidiuretic Action of Morphine on Mercurial Diuresis.* (C. P.) Closed circles represent the control curve with mercupurin alone. Open circles represent the curve under the influence of morphine. The axis of abscissæ represents the time in minutes after the mercupurin injection, and the axis of ordinates the urine flow in cc. per minute, chloride excretion rate in milliequivalents per minute, and chloride concentration in milliequivalents per liter. The arrow marks the time of morphine injection on the open circle curve. The antidiuretic effect begins 40 minutes after morphine is injected and is maximal at 120 minutes after morphine.

either during the control diuretic period with mercupurin alone, or following mercupurin and demerol. During the anti-diuretic effect of morphine in this patient there was a definite fall in urine chloride concentration (Fig. 5). This fall was not

demonstrated by the first patient whose chloride concentration remained constant during morphine antidiuresis.

A third patient (M. H.) was studied once with morphine. A control curve was also obtained. This patient showed a

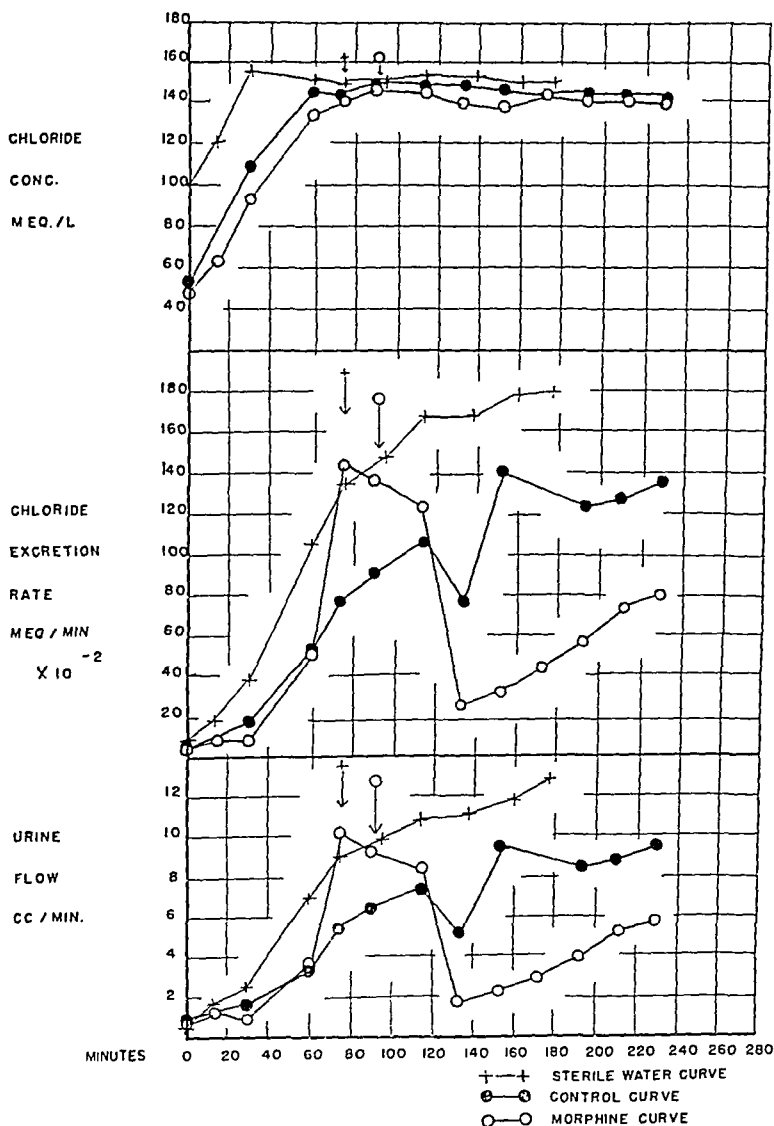


FIG. 2.—*The Antidiuretic Action of Morphine on Mercurial Diuresis.* (C. P.) These 3 diuretic curves are made on the same patient. Closed circles represent the control curve with mercupurin alone. Open circles represent the curve showing the influence of morphine and the cross marks a curve, showing the lack of influence of a sterile water injection on the mercurial diuretic curve. The arrow with the circle above it represents the time of injection of morphine on the open circle curve. The arrow with the cross mark above it represents the time of injection of the sterile water. The axis of abscissæ represents the time in minutes after the mercupurin injection, and the axis of ordinates the urine flow in cc. per minutes, chloride excretion rate in milliequivalents per minute, and chloride concentration in milliequivalents per liter.

somewhat less marked antidiuretic effect with morphine. The urine flow fell from 3.24 cc. to 2.03 cc. per minute. Demerol was not studied in this patient.

The 2 patients who showed an antidiuretic effect on 3 separate occasions demonstrate the consistent nature of this effect and rule out any possible chance phenomenon.

There were 6 cardiac patients who showed no antidiuretic effect with morphine during mercurial diuresis. It should be noted that perhaps a larger dose of morphine would have given an antidiuretic effect in these patients.

*Normal Subjects.* The first normal subject (F. St.C, Fig. 6) received the second administration of water by mouth: 1000 cc.

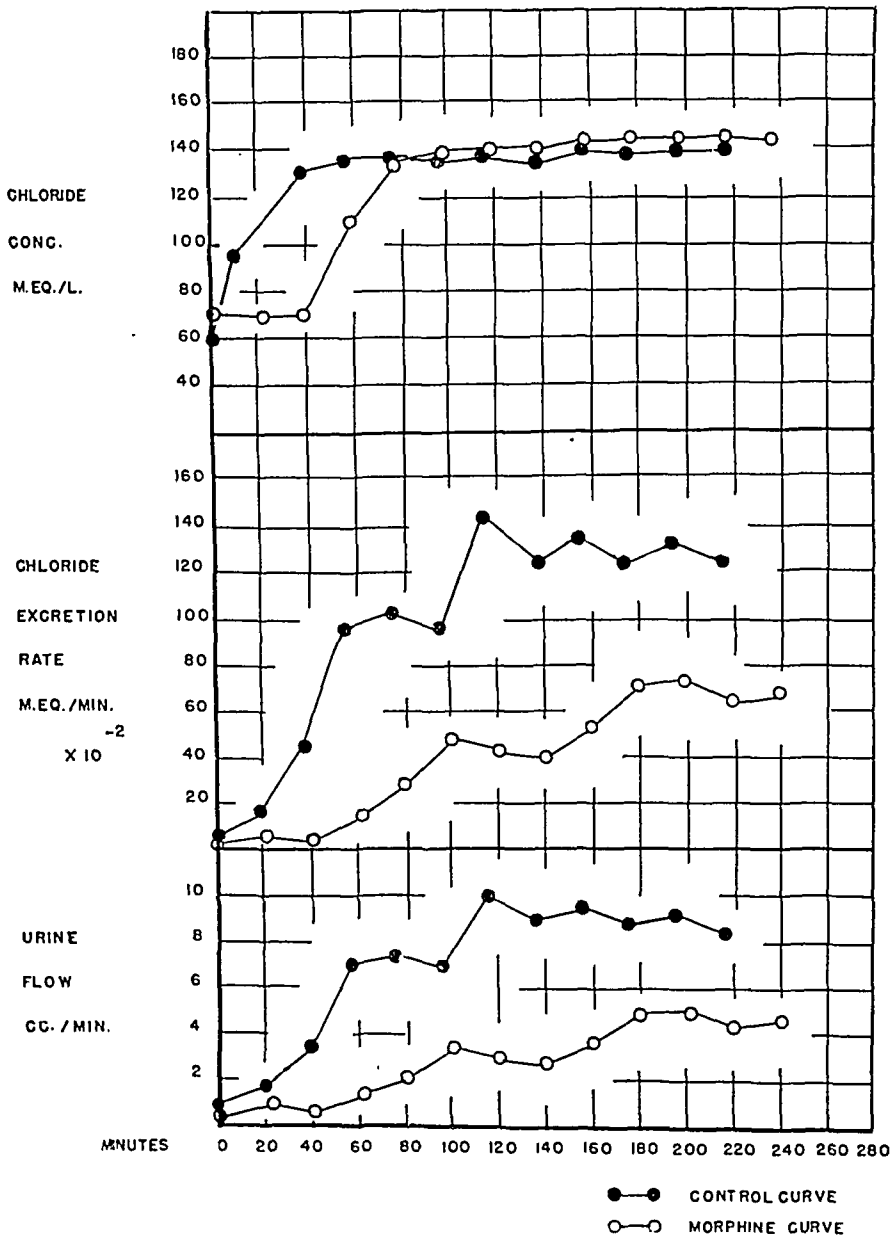


FIG. 3.—*The Antidiuretic Action of Morphine in Mercurial Diuresis.* (C. P.) Morphine sulfate was given 10 minutes before the mercurpurin in this study. Note the generally low diuretic curve that followed and which had not risen to the control level at the end of 4 hours. Closed circles represent the curve with mercurpurin alone. Open circles mark the curve under the influence of morphine. The axis of abscissæ represents the same in minutes after the mercurpurin injection and the axis of ordinates, the urine flow in cc. per minute, chloride excretion rate in milliequivalents per minute, and chloride concentration in milliequivalents per liter.



in 5 minutes. Twenty minutes after the water was given she received 0.01 gm. of morphine intramuscularly. Forty minutes after morphine was given, and 60 minutes after the second ingestion of water, there was a marked drop in the urine flow; from 4.8 cc. to 1.33 cc. per minute. As can be seen in Figure 6, the control diuretic curve made 2 days later

on this patient, with only the second ingestion of water (no morphine) shows that at 60 minutes after the second water the urine flow had risen to 8.4 cc. per minute. The antidiuretic effect of morphine in this patient continued for over 2 hours after the morphine was given. At the end of 3 hours the control period yielded 114% of the second water as

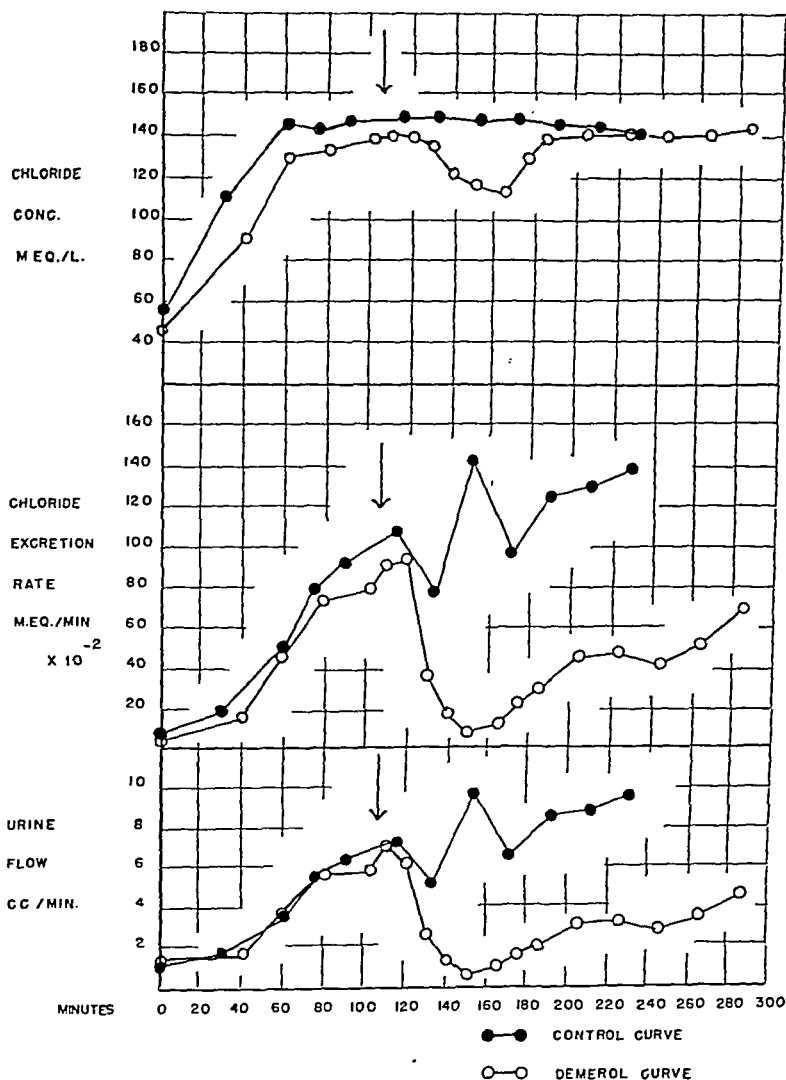


FIG. 4.—*The Antidiuretic Action of Demerol on Mercurial Diuresis.* (C. P.) Seventy-five mg. of demerol were given intramuscularly at the time marked by the arrow. Closed circles represent the control curve with mercupurin alone. Open circles represent the curve under the influence of demerol. The axis of abscissæ represents the time in minutes after the injection of mercupurin and the axis of ordinates, the urine flow in cc. per minute, chloride excretion in milliequivalents per minute, and chloride concentration in milliequivalents per liter. A slight fall in urine chloride concentration was noted during the antidiuretic effect of demerol.

urine returned. This demonstrates the fact that the patient was completely hydrated by the first water given. Under the influence of morphine only 70 % of the second water was recovered in the urine. It will also be noted in Figure 6 that the urine chloride concentration rose markedly during the antidiuretic action of

uride excretion in 3 hours was greater with morphine, being 19 milliequivalents (1.11 gm.), while the control excretion was 2.8 milliequivalents (0.17 gm.). Therefore, the total urinary chloride excretion increased during the period of morphine action.

Morphine, however, in some subjects,

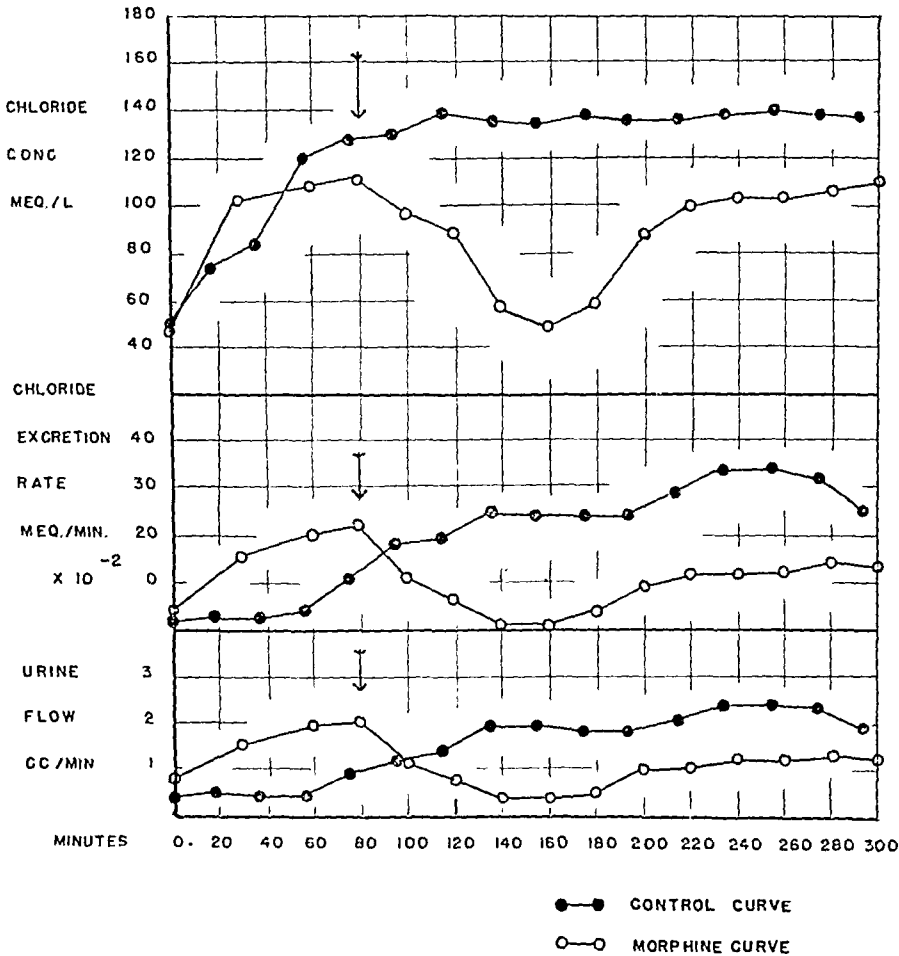


FIG. 5.—*The Antidiuretic Action of Morphine on Mercurial Diuresis.* (S. W.) Ten mg. of morphine sulfate was injected at the time marked by the arrow on the open circle curve. The closed circles represent the control curve with mercuripurin alone. The open circles delineate the curve under the influence of morphine. The axis of abscissæ represents the time in minutes after the injection of mercuripurin, and the axis of ordinates the urine flow in cc. per minute, chloride excretion rate in milliequivalents per minute and chloride concentration in milliequivalents per liter. Note the fall in urine chloride concentration during antidiuresis.

morphine. An initial level of 35.8 milliequivalents per liter rose to a maximum of 90 milliequivalents per liter, while control levels started at 13.3 and fell to 1.3 milliequivalents per liter during the control diuretic period. The chloride excretion rate was higher with morphine than the control rate, and the total chlo-

may hinder the absorption of water from the alimentary canal and the decreased excretion reflects this fact rather than true antidiuretic action. Thus, while water diuresis usually reaches its peak 40 to 60 minutes after water is taken, suggesting that the greater part of this water has been absorbed by this time, we were

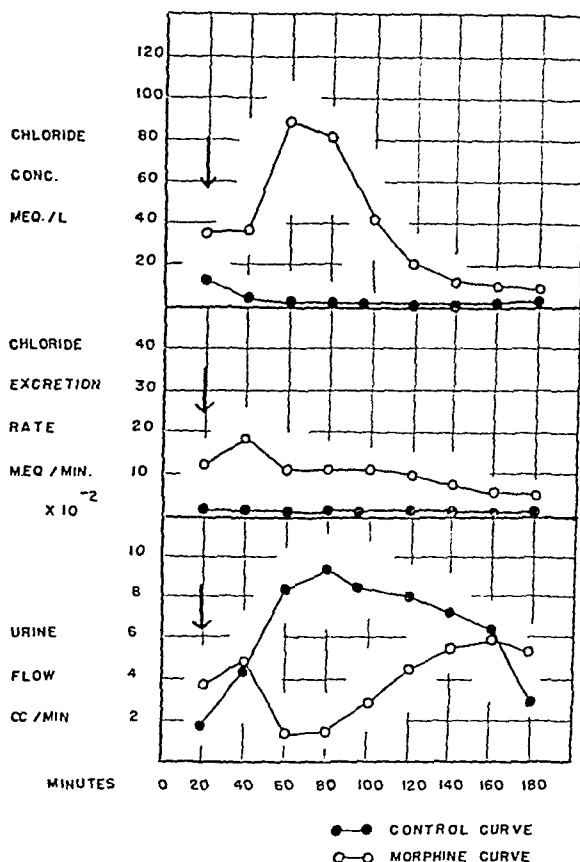


FIG. 6.—*The Antidiuretic Action of Morphine on Water Diuresis.* (F. St.C.) The arrow marks the time of the morphine injection. Closed circles represent the control curve of simple water diuresis. Open circles represent the influence of morphine on the water diuresis. The axis of abscissæ represents the time in minutes after the second water was administered, and the axis of ordinates the urine flow in cc. per minute, chloride excretion rate in milliequivalents per minute, and chloride concentration in milliequivalents per liter. Note the rise in urine chloride concentration during the antidiuretic action of morphine.

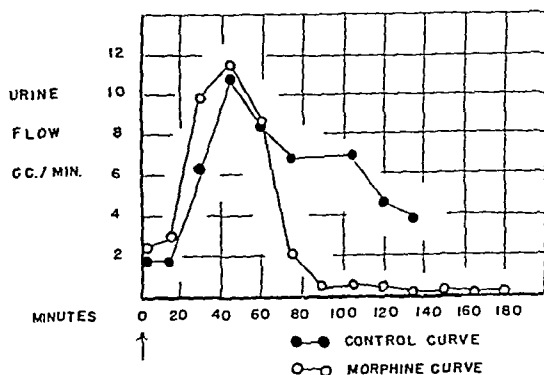


FIG. 7.—*The Antidiuretic Action of Morphine on Infusion Diuresis.* (M. McC.) The arrow marks the time of the morphine injection. Closed circles represent the control curve with simple infusion diuresis. Open circles mark the curve showing the influence of morphine on the infusion diuresis. The axis of abscissæ represents the time in minutes after the infusion was started. The axis of ordinates marks the urine flow in cc. per minute.

able to recover from the stomach of 1 normal subject 525 cc. of a 1000 cc. dose of water during this period, which was also 20 minutes after 0.015 gm. of morphine sulfate was administered intramuscularly.

In our patient, F. St.C. (Fig. 6), however, the urine chloride concentration rose during the antidiuresis and this indicated that the fall in water output was not due simply to diminished absorption from the gastro-intestinal tract. Therefore, these observations probably demonstrate true inhibition of water diuresis by morphine.

In using the intravenous route it would not be safe to give a large dose of unmodified distilled water rapidly. For this reason distilled water was given with 5% glucose. Under these conditions, however, we are no longer dealing with a simple water diuresis. Three normal subjects were studied using this method.

The second normal subject, M. McC. (Fig. 7), received the second water as 1000 cc. of 5% glucose in water given in 40 minutes. Since the factor of absorption plays no rôle in the fluid administration here, the morphine sulfate, 0.01 gm. was given at the same time as the infusion was started. Sixty minutes after morphine was given, urine flow was 8.6 cc. per minute (Fig. 7). Seventy-five minutes after morphine (this is also 75 minutes after the infusion was started) the urine had fallen to 2.2 cc. per minute and at 90 minutes after morphine the urine flow fell to 0.6 cc. per minute and remained under 0.5 cc. per minute until the study was completed 3 hours after morphine was given. A control curve obtained 1 week before remained between 6.7 and 3.8 cc. per minute from 75 to 135 minutes ( $2\frac{1}{2}$  hours) after the infusion was started. In this patient no chloride determinations were made.

In a third subject morphine was given 1 hour before the infusion was started in order to learn if the diuresis could be suppressed before it had been initiated. This patient showed no antidiuretic effect and excreted 102% of the 1000 cc. in 2 hours after the infusion was started.

A fourth subject received the morphine 70 minutes and 15 minutes before the infusion on 2 separate occasions. A control curve was also obtained. Morphine had no apparent effect on these 2 occasions.

The antidiuretic effect, therefore, was noted in 2 of the 4 normal subjects studied. Again it should also be noted that the dose of morphine used here was relatively small and conceivably a larger one might have made the antidiuretic effect apparent.

**Discussion.** That morphine inhibits diuresis due to water has been firmly established in several animal species. The demonstration that it has a similar action in humans presents great technical difficulties. To initiate diuresis, one may administer the water by mouth or intravenously, as was done in this study. In the first place, when water is given by mouth, it may be possible to demonstrate a decrease in water excretion during the period of morphine action. This is noted in Fee's study<sup>16</sup> and in our own patient (F. St.C., Fig. 6). In our patient the rise in chloride excretion is a further check on the morphine action. It must be remembered, however, that all of the water may not be absorbed, as demonstrated in the patient studied by means of stomach tube, who still had over half the initial water dose in the stomach 40 to 60 minutes after it was given. Decreased percentual return of the water thus cannot be used as an evidence of morphine action, unless a check of the amount of water leaving the stomach is made. In the second group of normals studied, true simple water diuresis was not established, as glucose in itself influences diuresis.

However, from the results obtained it is apparent that morphine and demerol exert an antidiuretic effect on mercurial diuresis in some patients with congestive heart failure. Morphine was also shown to inhibit a simple water diuresis and an infusion diuresis in some normal persons. The antidiuretic effect was noted as early as 40 minutes and as late as 75 minutes after morphine was given and persisted for a period of  $2\frac{1}{2}$  to 4 hours. The anti-

diuretic effect of demerol was noted somewhat sooner, 24 minutes after the injection, and persisted 2 to 3 hours.

It was of clinical interest that 1 cardiac patient (C. P., Figs. 1 to 4) reported to us after the study that before she came under our care her physician had sedated her with frequent oral tablets of morphine and that injections of mercupurin did not result in diuresis. Another cardiac patient (S. W., Fig. 5) volunteered the information that diuresis was delayed for 12 hours when she had been given morphine with the mercupurin.

*Mechanism of the Antidiuretic Action.*

Renal ischemia might be suspected, as it is known that morphine causes liberation of epinephrine<sup>14</sup> in dogs and epinephrine can cause diminished renal blood flow. De Bodo,<sup>12</sup> however, disproved this mechanism by showing that in dogs, with 1 adrenal gland extirpated and the second denervated, morphine caused inhibition of water diuresis to the same extent as in the normal dog. In our patient (S. W.) there was no change in renal plasma flow during the antidiuretic period. This type of renal function study during narcosis, as done by Corcoran and Page<sup>9</sup> and Craig, Visscher and Houck,<sup>10</sup> has been criticized recently by de Bodo<sup>13</sup> because agents in themselves influencing diuresis (such as glucose, saline, etc.) have been included in the infusion material. Fee, in 1928, suggested a mechanism involving the pituitary. De Bodo is of the opinion that morphine inhibits water diuresis by an action upon the hypothalamic-hypophyseal system, probably by increasing the secretion or liberation of the antidiuretic hormone. He and his co-workers,<sup>11,12,13</sup> working on dogs, carried out a careful differentiation of the regions of the pituitary that were necessary for the antidiuretic action of morphine. Their work suggested that a functioning neurohypophysis was necessary for this action. The liberation of this pituitary hormone could be a release phenomenon, or morphine could stimulate the hypothalamic-hypophyseal system either by action on

the supra-optic or para-ventricular nuclei or on the pituitrin secreting cells themselves. The intimate details of the mechanism are, of course, not yet known. Pickford,<sup>29</sup> in a recent review, is of the opinion that the pituitary mechanism need not represent the sole explanation of the antidiuretic action.

*Chloride Excretion.* De Bodo concludes that morphine achieves its antidiuretic action by means of the antidiuretic hormone and bases this conclusion firstly on the fact that morphine and the hormone have analogous actions on water diuresis. In enlarging on this analogous action, he further points out that the neurohypophyseal antidiuretic hormone brings about a percentual and absolute increase in urinary chloride excretion. The chloride increase was also noted in dogs during morphine antidiuresis. A third point of similarity of action between the antidiuretic hormone and morphine is that neither reagent inhibits saline diuresis as a rule, but if any suppression occurs it is of a lesser degree than in water diuresis. In summary, therefore, morphine in animals appears to have the same effect on water diuresis, chloride excretion, and saline diuresis as the antidiuretic hormone, all points in favor of the action of morphine being due to the liberation of the hormone. Saline diuresis in dogs is not affected by morphine. This does not appear to be the case with phenobarbital which, in some animals, does inhibit saline diuresis.

In 2 of the 4 studies of water diuresis in man, morphine exerted an antidiuretic effect. Morphine also brought about an increase in total urinary chloride excretion in 1 patient so studied; 2.79 milliequivalents (0.166 gm.) during the control 3 hours, and 19 milliequivalents (1.11 gm.) during the morphine effect (F. St.C, Fig. 6). In the studies with mercurial diuresis, however, entirely different results with chloride excretion were obtained.

In man, the normal concentration of urinary chloride is about 102.5 milli-

equivalents per liter or 6 gm. per liter. The 24 hour chloride excretion of a normal adult studied for 16 consecutive days fluctuated between 60 and 130 milliequivalents or 3.5 and 7.7 gm.<sup>20</sup> In a 4 hour period, therefore, the estimated total chloride excreted would be 10 to 22 milliequivalents or 0.58 to 1.28 gm. of chloride. In man, diuresis following mercurials is known to be accompanied by a marked increase in chloride excretion. In our patients, the concentration of urinary chloride rose markedly from a control range of 50 to 70 milliequivalents (2.92 to 4.08 gm.) per liter before mercupurin was given, to a range of 100 to 150 milliequivalents (5.8 to 8.77 gm.) per liter

concentration in the urine. In all 3 patients, however, the total chloride excreted in the urine during the antidiuretic period as compared with each control period was considerably reduced. Results are outlined in Table 1.

The normal chloride excretion during any 4 hour period of the day has been estimated as 10 to 22 milliequivalents (0.58 to 1.28 gm.). Comparison of this figure with the total chloride excreted the 4 hours following the injection of mercupurin (see Table 1) emphasized the large mobilization of chloride affected by mercupurin. This mobilization of chloride, as measured in our observations by the total chloride excretion during the period

TABLE 1.—THE EFFECT OF MORPHINE AND DEMEROL ON CHLORIDE EXCRETION DURING MERCURIAL DIURESIS IN MAN

Patient	Control diuretic curves	During morphine antidiuresis	During demerol antidiuresis
<i>Total Chloride Excreted in the Urine During 4 Hours Following Mercupurin</i>			
C. P. . . . .	255.0 m.eq. (14.9 gm.)	171.2 m.eq. (10.0 gm.)	102.9 m.eq. (6.0 gm.)
	219.0 m.eq. (12.8 gm.)	159.7 m.eq. (9.34 gm.)	
	314.2 m.eq. (18.35 gm.)	104.5 m.eq. (6.1 gm.)	
M. H. . . . .	155.5 m.eq. (9.08 gm.)	74.5 m.eq. (4.35 gm.)	
<i>Total Chloride Excreted in the Urine During 5 Hours Following Mercupurin</i>			
S. W. . . . .	63.3 m.eq. (3.7 gm.)	18.4 m.eq. (1.08 gm.)	
	57.6 m.eq. (3.36 gm.)		

following mercupurin. (Figs. 1 to 5.) This elevated concentration was reached early, usually within the 1st hour after mercupurin was injected and occasionally before diuresis was noted, and was maintained at a constant level throughout the next 3 to 4 hours. In 2 of the 3 patients showing an antidiuretic effect the urine chloride concentrations remained approximately the same during antidiuretic as during the control periods. In 1 patient following morphine (S. W.) the chloride concentration fell to the control levels obtained before mercupurin was given and only rose again at the end of the antidiuretic effect. Morphine, in this case, therefore, caused a decrease in the chloride

of study, was considerably reduced during morphine and demerol antidiuresis.

In our observations in man, morphine caused an antidiuretic effect and a slight increase in chloride excretion during the studies on water diuresis. This agrees favorably with De Bodo's animal studies. It is apparent, however, that morphine had a similar antidiuretic effect on mercurial diuresis but a depressant effect on chloride excretion during this diuresis. If mercurial diuresis can be considered at least in part a saline diuresis, then in man it can be said that morphine does depress or inhibit saline diuresis.

**Conclusions.** 1. The influence of morphine on mercurial diuresis was studied in

9 patients with congestive heart failure. In 3 morphine produced an antidiuretic effect. In 2 patients demerol also showed an antidiuretic effect.

2. The total chloride excretion during mercurial diuresis was reduced by morphine and demerol.

3. Under certain circumstances it is possible to demonstrate the inhibition of water diuresis in man by morphine. The

total chloride excretion during water diuresis was increased by morphine.

4. It is suggested that the antidiuretic effect of morphine and demerol, while probably not operative in all patients, cardiacs or otherwise, is of sufficient importance in some cases of cardiac decompensation to account for certain poor results with mercurial diuretics.

The authors would like to express their thanks to Dr. Arthur C. DeGraff for his suggestions and help which he has given us in this work.

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## FAILURE OF STREPTOMYCIN IN THE TREATMENT OF LEPROSY

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THE ability of streptomycin to inhibit the growth of *Mycobacterium tuberculosis*, *in vivo* and *in vitro*, has been demonstrated by numerous investigators.<sup>1-5</sup>

Because *Mycobacterium lepræ* resembles *M. tuberculosis* in its morphology, staining qualities and in its tendency to produce chronic granulomata, it seemed reasonable to attempt the treatment of leprosy with streptomycin, after no report of this use of streptomycin could be found in the literature.

**Case History.** P. O., a Filipino steward's mate, was admitted to the hospital on Sept. 14, 1946, complaining of areas of dark and of depigmented skin over legs and trunk. He stated that while working in Guam in July 1946, he had stumbled into mud up to his knees while carrying a heavy box, and shortly after noted an itching and scaling of both legs. The lesions spread downward over the feet and upward to his knees. In August 1946, he noted that patches of skin over his chest were losing their normal pigmentation. The past medical history was not remarkable, save that he had been bitten by a dog in 1944. He enlisted in the Navy as a steward's mate in the Philippine Islands on May 29, 1946, at which time no physical abnormalities of the skin were noted in his health record, and the patient stated that none existed.

A family history failed to show any instances of leprosy in the immediate or collateral relatives, nor did he remember any contact with any known leper.

The physical examination, at the time of admission, was normal, save for depigmented macules scattered over the trunk, back, arms, buttocks and thighs; infiltrated flat brownish-red plaques over the lateral borders of the feet, and the posterior aspects of the heels; and scaling ichthyotic pigmented plaques over the shins. There was a healed ulcer, 3 cm. in diameter, on the medial aspect of the left leg, 10 cm. above the internal

malleolus. There was bilateral inguinal adenopathy. On the first examination there was no evidence of weakness, or wasting of any of the skeletal muscles. No thickening of the peripheral nerves could be found, and there were no areas of anesthesia.

The following investigations were made: Urine: sp. gr. 1.011; reaction, acid; albumin and sugar, negative. Microscopic examination: no abnormalities. A complete blood count was within the limits of normal; RBC, 4,900,000; hemoglobin, 14 gm. (97%); WBC, 8900 (neutrophils, band forms, 2; segmented, 56; lymphocytes, 35; eosinophils, 7). The blood Kahn test was negative. The blood sedimentation rate was 5 mm. in 1 hour.

A roentgenogram of the chest showed moderate prominent bronchovascular markings along the right border of the heart. There was no evidence of active disease of the parenchyma, although the right apex was slightly more dense than the left, which was interpreted as being due to thickening of the pleura. The transverse diameter of the heart was within the limits of normal, and the great vessels were not unusual.

The clinical evidence suggested a diagnosis of leprosy. Scrapings of the nasal mucous membrane and stains of serum obtained from nodular lesions failed to show acid fast organisms. A tuberculin test, on Sept. 23, 1946, using purified protein derivative, in the second dilution was positive in 48 hours. On September 21 a similar test with purified protein derivative in the first dilution, was negative in 48 hours. On September 27, it was demonstrated that the depigmented macular areas on the trunk were hypesthetic. Repeated attempts were made to obtain *M. lepræ* from the nasal mucous membranes and from the nodular and depigmented macular lesions of the trunk and extremities without success. A biopsy was obtained from a nodular lesion on the left leg, and on November 1 acid fast organisms were demonstrated in sections obtained from this material. Because of the clinical evidence of leprosy and the finding of acid fast organ-

\* This work was done while serving as Chief of Medicine, United States Naval Hospital, Treasure Island, San Francisco.



isms in the skin, no attempt was made to cultivate the organism on artificial media or in animals. Photographs were taken of the lesions of the skin (Fig. 1). A reëxamination of the patient, at this time, revealed areas of anesthesia over the right foot, and over the depigmented macular areas of the trunk and extremities. There were depigmented macules scattered over the back, arms, but-

hands, and loss of tone with slight flattening of the hypothenar eminence of the right hand, and atrophy of the muscles of the second interosseous space of the right hand was noted. There was slight drooping of the lower right eyelid. No thickening of the peripheral nerves could be demonstrated. The sedimentation rate was 15 mm. in 1 hour. The complete blood count was similar to the

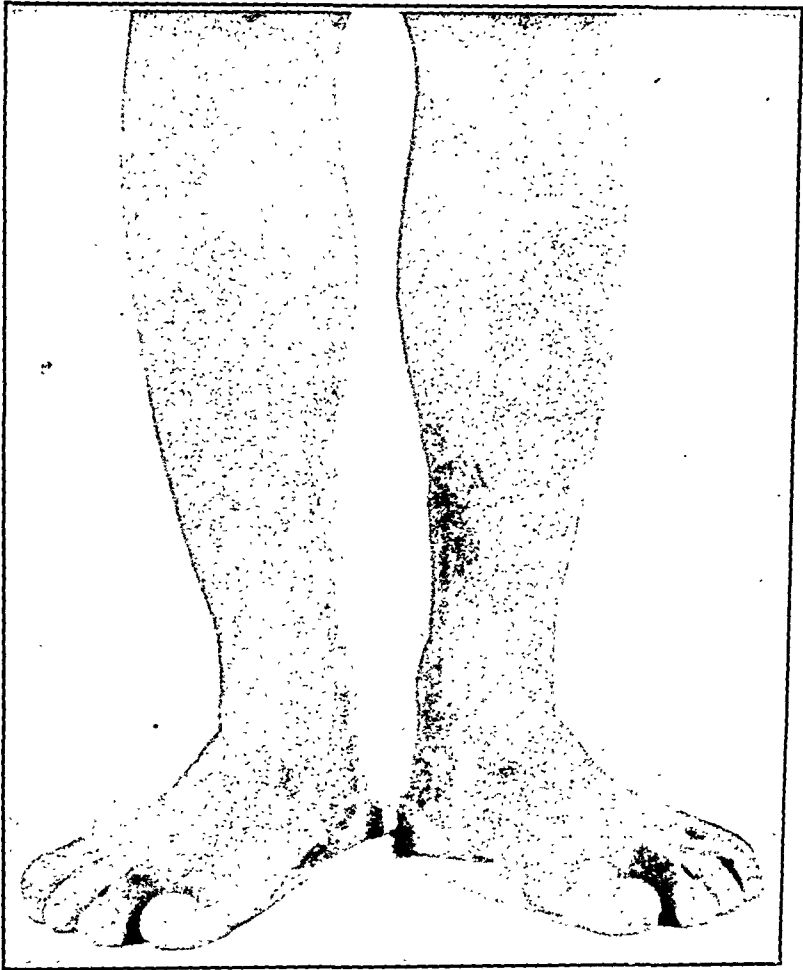


FIG. 1.—Photograph illustrating ichthyotic plaques over the shins before treatment.

tocks and thighs, and infiltrated brownish-red plaques over the lateral borders of the foot, posterior aspect of the heel, and an occasional macule on the buttocks. There were ichthyotic plaques over the shins and hypesthesia approaching anesthesia of the skin, of the lesions, on the buttocks and thighs, and of the lateral and posterior aspects of the feet. A slight cyanosis of the

one taken on admission, and a second blood Kahn test was negative. On November 1, streptomycin therapy was started. The patient was given an intramuscular injection of 4 gm. of streptomycin as an initial dose; and 2 gm. were given intramuscularly every 2 hours for 72 hours, followed thereafter by 0.5 gm. every 4 hours, throughout the course of treatment. On November 2 he com-

plained of severe vertigo when attempting to stand erect or walk. On November 5 the sedimentation rate was 11 mm. in 1 hour. On November 7 the vertigo had subsided and it was noted that the scaling lesions over the legs were disappearing and the epidermis appeared nearer normal. The areas of hyperpigmentation and depigmentation were unaffected. At this time, the

the sedimentation rate was 2 mm. in 1 hour. On November 29 the patient complained of pain in both external ears, and areas of hyperpigmentation were noted along the helices. On December 7 he complained of some dizziness, as well as pain over the nodular lesions on the skin, which appeared to be darker in color. On December 18 he complained of pain in the lobule of the right

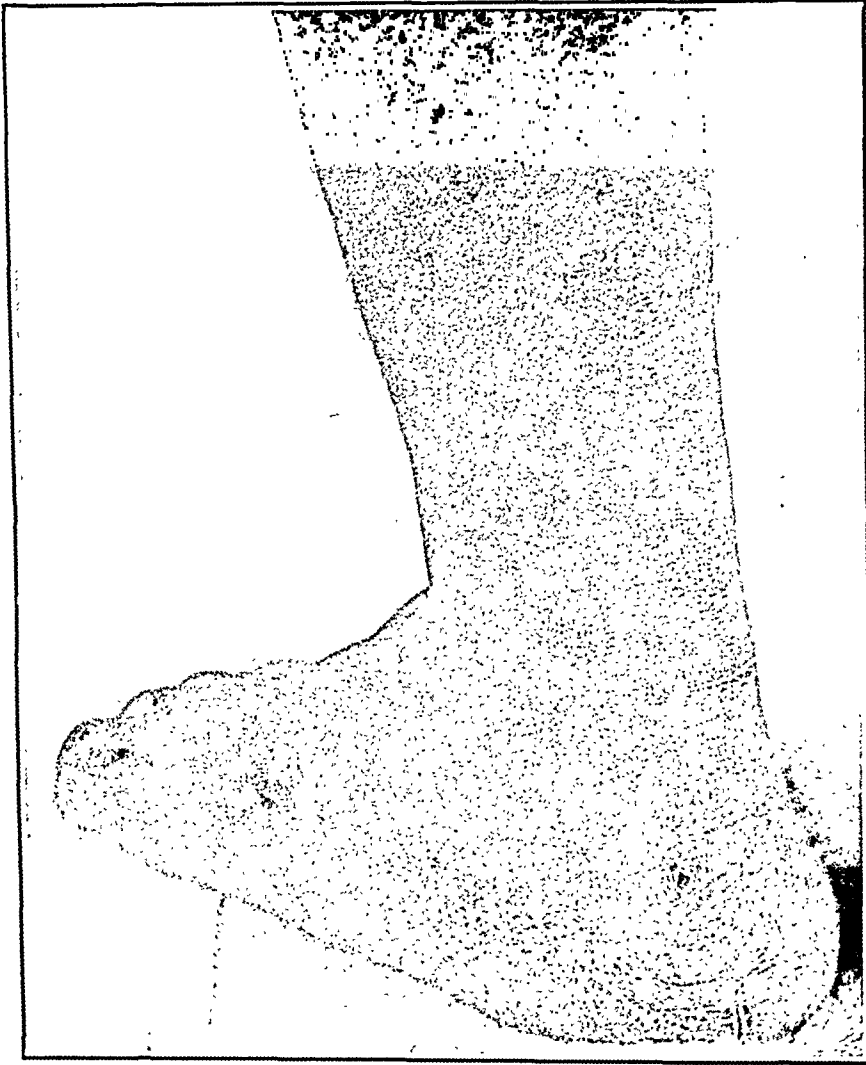


FIG. 2.—Left foot showing hyperpigmented nodular lesions and the remains of the ichthyotic plaques following therapy with streptomycin.

patient noted some pain in the areas of hyperpigmentation, about the bases of the toes, and the dorsal surfaces of both feet. There was no change in the neurologic examination. On November 19, photographs were taken of the lesions of the skin (Fig. 2). It was noted that the hyperpigmented areas over the feet had become anesthetic and had increased in size. The ichthyotic lesions continued to improve. On November 20

ear, where a nodule had formed. He stated that the pain was worse when the room was warm. On December 10 the patient was seen by Dr. N. E. Wayson, Medical Director of the U. S. Public Health Service, who confirmed the diagnosis of leprosy. On December 26 streptomycin was discontinued. The patient had received 175 gm. of streptomycin over a period of 55 days. On December 31 all evidence of vertigo had subsided

and a biopsy was obtained from a lesion similar to, and adjacent to the lesion from which the original biopsy was taken. The tissue obtained at this time showed acid fast organisms morphologically resembling *M. lepræ* in approximately the same number and distribution, as those seen in the original biopsy. By Jan. 13, 1947, the ichthyotic areas over both shins had returned, and resembled the lesions prior to the beginning of treatment. On February 1 it was decided that the trial of therapy with streptomycin had been unsuccessful, and arrangements were made for the transfer of this patient to the leprosarium at Carville, Louisiana.

**Summary.** 1. A patient suffering from leprosy in a relatively advanced and apparently progressive stage was treated with 175 gm. of streptomycin over a period of 55 days.

2. Ichthyotic lesions over the anterior surfaces of both legs showed improvement,

but returned when streptomycin was discontinued.

3. The sedimentation rate dropped from 15 mm. in 1 hour to 2 mm. in 1 hour, during the course of therapy, but returned to 11 mm. in 1 hour, 1 month after treatment was discontinued.

4. Biopsies obtained before and after treatment showed acid fast organisms morphologically resembling *M. lepræ* in approximately equal numbers and distribution.

5. Depigmented macular and hyperpigmented nodular lesions progressed in spite of therapy.

6. Vertigo was the only toxic manifestation noted from the streptomycin.

**Conclusion.** The course of leprosy in this patient was not significantly altered by treatment with large doses of streptomycin.

It is my pleasant duty to thank George G. Herman, Capt. (MC) USN, for his permission to carry out these studies; N. E. Wayson, Col., U. S. Public Health Service, for his kind suggestions and help; and D. Osborne, Lt. Comdr. H(W), for the histologic sections used in this study.

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## PSITTACOSIS

## REPORT OF AN OUTBREAK

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PSITTACOSIS is a rare disease in Massachusetts. From August 1938, the date it was declared a reportable disease, to April 1946, when the outbreak to be described in this report occurred, not a single case had been recorded. However, from December 1929 to March 1930, a series of 15 cases came to the attention of the Massachusetts Department of Public Health. Investigation revealed that each patient had been exposed to infected parrots in one or another of 2 pet shops. Three sporadic cases had been noted prior to 1938, 2 in 1932 and 1 in 1934.

It is difficult to obtain a reliable estimate of the true incidence of psittacosis. Unless a history of exposure to psittacine or other birds which may transmit the infection is elicited, cases of ornithosis may not be recognized. Routine testing of acute and convalescent phase sera obtained from cases of virus pneumonia for the presence of psittacosis complement fixing antibodies would result in the recognition of additional cases. Similarly, ornithosis caused by psittacosis-like agents of non-psittacine derivation are equally difficult to detect.

Clinically ornithosis resembles atypical pneumonia to such an extent that confusion in the diagnosis of these diseases is quite understandable. At times the pulmonary involvement that occurs in both conditions is demonstrable only by Roentgen ray. The white blood count and the clinical course may be similar and of limited value in the differential diagnosis. For these reasons, without special labora-

tory aids, it is possible that cases of ornithosis may be misdiagnosed as virus pneumonia.

It is proposed in this discussion to present the clinical, laboratory and epidemiologic aspects of a small outbreak of psittacosis which occurred in Massachusetts during April and May 1946. Serologic tests revealed a possible third case in a person who had been exposed to birds in 1 of the aviaries concerned in the outbreak. Blood specimens from 2 other exposed persons who had not been ill were positive in a low dilution, suggesting inapparent infection.

**Case Reports.** CASE 1. Mrs. C. E., a 44 year old, white, married housewife, was referred on April 24, 1946, to the Faulkner Hospital, Boston, Mass., under the care of Dr. Channing Frothingham, with a complaint of recurrent daily fever that had risen as high as 103° F. She had been quite well until about 4 days before admission when she noticed the onset of slight fever, general malaise and headache. Three days later the elevated temperature and headache were still present and the patient had developed generalized muscle pain. She gave no history of cough, dyspnea or recent upper respiratory infection. Chest pain and other symptoms of pneumonia were lacking.

**Physical Examination.** The patient presented the picture of an acute infection with hot, dry skin, anxious expression and marked prostration. The temperature was 103° F., pulse rate 100 and respiratory rate 22. General physical examination was negative.

**Laboratory Studies.** A blood culture, upon admission before treatment was instituted,

showed no growth. The white count was 7800 with a normal blood smear. Subsequent white counts on April 28 and 30 were 5100 and 7100 respectively, with normal blood smears. All urine and stool examinations were negative. Roentgen ray of the

chest was reported by Dr. Harvey Morrison as follows: "The findings are those of 3 areas of pneumonic infiltration, 1 in the right upper lobe, 1 in the left upper lobe and the third in the left lower lobe. The appearance is more that of an atypical pneumonia,

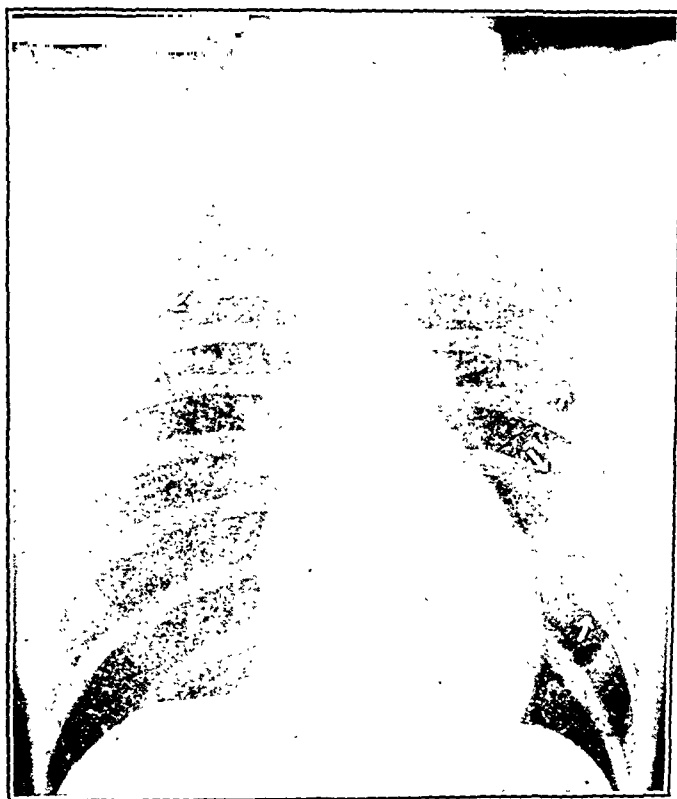


FIG. 1.—Chest Roentgen ray of Mrs. C. E. (Case 1) showing 3 areas of pneumonic infiltration as indicated by the arrows.

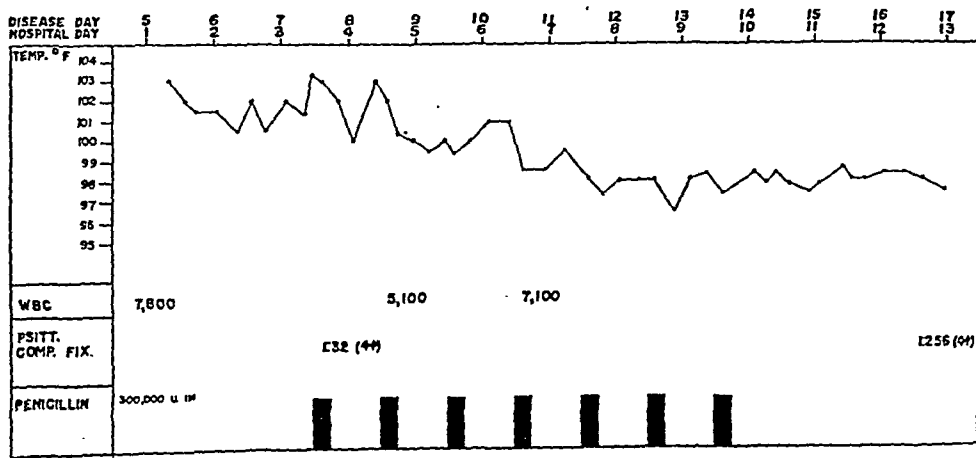


FIG. 2.—Clinical chart of Mrs. C. E. (Case 1).

although such unusual types of pneumonia as eosinophilic pneumonia cannot be excluded. There is nothing inconsistent with psittacosis." (Fig. 1.)

Blood samples for psittacosis complement fixation tests, sent to Dr. K. F. Meyer of California, were reported as follows:

Date sample taken	Titer
April 27 . . .	1:32 4+, 1:64 2+
May 6 . . .	1:256 4+, 1:512 2+
June 1 . . .	1:512 4+

*Clinical Course.* Treatment with penicillin was instituted on the 3rd hospital day; 300,000 units in beeswax and peanut oil were administered daily for 7 days. The temperature dropped slowly by lysis and within 4 days had returned to normal. (Fig. 2.)

There was no cough throughout the entire illness and no physical findings suggestive of pneumonia. On the 3rd day of hospitalization the patient complained of some pain in the left chest upon deep inspiration. The heart rate seemed to be relatively slow despite the elevated temperature. The patient's complaints of headache and muscle pain gradually disappeared and the temperature fell. Appetite and general well-being returned slowly and she was discharged on the 12th day.

CASE 2. Mr. A. M., a 31 year old, white male, entered the Cambridge Hospital, Cambridge, Mass., on April 30, 1946, with a history of severe headache and chills for 5 days. Four days prior to admission he was unable to continue at work and upon arrival at his home his temperature was found to be 103° F. The headache persisted without relief. There was moderate anorexia, but no other unusual symptoms. On the 7th day of his illness, the patient had diaphoresis associated with a remission of the fever. There had been a very slight, infrequent cough without chest pain, sputum, dyspnea or orthopnea.

*Physical Examination.* On admission the temperature was 102.6° F., pulse 100, respiration 28. Patient was a very well-developed and well-nourished male in no acute distress. The physical examination was essentially negative.

*Laboratory Studies.* Initial blood study: red blood count 4,320,000, hemoglobin 91% (Sahli); white blood count 6500 (neutrophils 68%, lymphocytes 29%, monocytes 3%).

Urinalysis and the Hinton test were negative. On April 30 blood culture showed *S. albus* (probably a contaminant). Roentgen ray of chest on May 1 was read as follows: "There is some bronchitis at the right base. The lungs are otherwise normal. The heart is normal." A repeat examination on May 8 was read: "Reexamination shows a definite improvement in the infectious process involving the right lower lobe."

Blood samples for psittacosis complement fixation tests were sent to Dr. K. F. Meyer and were reported as follows:

Date sample taken	Titer
April 30 . . .	1:2 4+
May 8 . . .	1:32 4+
June 11 . . .	1:64 4+, 1:128 3+, 1:256 2+

*Clinical Course.* The temperature remained elevated for 3 days. Repeated physical examination of the chest revealed no abnormal findings. The cough remained unproductive and gradually disappeared during the hospital stay. Recovery was uneventful and patient was discharged on May 10, 1946.

**EPIDEMIOLOGY.** The epidemiologic investigation revealed that both patients had been in contact with sick parakeets, several of which had died. A. E., husband of C. E. (Case 1), maintained an aviary (Aviary A) at his home. Both the husband and the wife cared for the birds. A. M. (Case 2) was a neighbor who had been exposed to the birds in this aviary on several occasions during the month prior to the onset of his illness. A sample of blood taken from A. E. showed a positive complement fixation test for psittacosis in a serum dilution of 1:64 4+, 1:128 3+. He had not been ill.

Several weeks prior to the occurrence of illness among birds of his aviary, A. E. had purchased several parakeets from the owner of another aviary (Aviary B). There had been several deaths among the parakeets in Aviary B. Recent additions of psittacine birds to both of these flocks had been made from aviaries outside of Massachusetts.

Investigation among persons exposed to Aviary B revealed that 1 individual, a

Dr. M., had developed a febrile illness associated with pulmonary signs and symptoms on Dec. 13, 1945. He had been hospitalized with a diagnosis of lobar pneumonia. A chest Roentgen ray taken during the hospital stay showed a shadow at the left base. The white blood count was 9000, with 68% polymorphonuclears. Blood specimens taken from this patient and Mrs. A, the owner of Aviary B, were sent to Dr. K. F. Meyer and were reported as follows: specimen from Dr. M. was positive in dilution of 1:16 4+, 1:32 2+; that of Mrs. A., 1:8 4+ and 1:16 2+. In the absence of the acute phase complement fixation test for psittacosis on Dr. M., the evidence that his illness was caused by the virus of psittacosis is only presumptive.

The National Institute of Health isolated the virus of psittacosis from a sick parakeet in Aviary A. The remainder of the birds in this aviary were destroyed. The birds in Aviary B were placed under quarantine for several months. No birds became ill during the period of observation. Two ricebirds, a species that are highly susceptible to the virus of psittacosis, were admitted to this aviary but did not develop psittacosis.

**Comment.** The paucity of reported cases of psittacosis may indicate either low incidence or failure of recognition. A study by Meiklejohn *et al.*<sup>8</sup> showed that when 250 specimens of sputum and lung tissue from patients with primary atypical pneumonia were inoculated into mice and cotton rats, only 10 positive isolations of psittacosis-like viruses were recorded. By use of the complement fixation test, 4 or 5 additional cases of psittacosis-like infection were found from which no virus was isolated. These findings suggest that psittacosis-like virus accounted for only a small portion of the total cases of primary atypical pneumonia.

Favour<sup>2</sup> in 1943 reported 3 cases of ornithosis in Massachusetts. The presumptive source of infection was canaries in 1 case and pigeons in another. No history of contact with birds could be es-

tablished in the third. In 1946 an additional case of ornithosis in a bird fancier who had been exposed to pigeons was reported to the Massachusetts Department of Public Health.<sup>13</sup>

It has been demonstrated that psittacosis is related antigenically to a virus recovered by Eaton, Beck and Pearson from the lungs of 2 fatal cases of atypical pneumonia.<sup>1</sup> Harrop, Rake and Shaffer showed that laboratory personnel, working with lymphogranuloma virus, developed atypical pneumonia.<sup>4</sup> Cross-reactions in the sera of these patients were found between the virus of psittacosis, the virus of lymphogranuloma venereum, the Eaton virus and Francis and Magill's meningo-pneumonitis virus.

Because of these cross-reactions, virus isolation should be attempted wherever possible in order to establish a definite etiologic diagnosis. Unfortunately, the present lack of laboratory facilities makes it difficult to attempt virus isolations from large numbers of patients with signs and symptoms suggestive of ornithosis. However, a careful history as to contact with birds, plus the use of acute and convalescent phase complement fixation tests in properly selected cases, is of considerable value in the recognition of ornithosis.

Human infections have been traced to canaries as well as psittacine birds.<sup>9</sup> Chickens, doves and many types of finches are also known to be infected.<sup>10</sup> Since 1941, when it was discovered that pigeons may transmit ornithosis,<sup>11</sup> an increasing amount of attention has been devoted to this species as possible vectors. Studies of pigeons from flocks or lofts in California, New York and South Carolina have resulted in successful isolations of psittacosis viruses.<sup>10</sup>

Two routes of transmission of infection from bird to man are possible. The first is *via* the respiratory tract and the second by direct contact with infected birds. Droppings of the parakeet, parrot, pigeon and fulmar, harbor the virus and may be responsible for respiratory invasion of man by dust. When canaries, finches and hens

are the source of infection the contact is usually direct as in handling of these birds.

Many persons, such as bird fanciers, breeders, pet shop owners and veterinarians, develop ornithosis as the result of occupational contact with birds. Apart from these occupational infections, the majority of reports deal with single or multiple cases in the households of people who have recently purchased infected birds. Children are less susceptible to infection than adults. It has been noted that children frequently escape infection following exposure to parakeets that have infected their parents or other relatives.<sup>10</sup> In rare instances human to human transmission has occurred.<sup>6,7</sup>

The control of psittacosis presents many difficulties. Although the importation of tropical psittacine birds may be regulated by quarantine measures, it is difficult to detect inapparent infections and parrots may be carriers of the virus for many months. Prolonged periods of isolation are essential.

Aviaries yielding infected birds are quarantined and necessary steps are then taken to destroy the entire flock and disinfect the premises. Because of the frequent interchange of birds by dealers and bird fanciers, it is often difficult to trace chains of infection from one aviary to another.

Latent infection in some aviaries may suddenly become activated when birds are subjected to overcrowding, insanitary conditions, changes in diet or unusual activities such as a change in locality.<sup>10</sup> Studies by the California Department of Public

Health revealed that the virus was present in many aviaries, the infection being either latent or active.

It will be noted that Mrs. C. E. (Case 1) was treated with penicillin, 300,000 Oxford units having been given each day for 7 days. Heilman and Herrell<sup>5</sup> showed the protective effect of penicillin on mice experimentally infected with a strain of psittacosis virus. Turgasen<sup>12</sup> and Flippin *et al.*<sup>3</sup> reported on the treatment of human cases of ornithosis with penicillin. However, no definite conclusions concerning the efficacy of penicillin should be drawn from these isolated cases. It is apparent that the second patient (Case 2) made an uneventful recovery without the use of penicillin.

**Summary.** An outbreak of psittacosis in Massachusetts is described. Positive complement fixation tests for psittacosis were obtained from 2 patients, 2 contacts without evidence of clinical disease and 1 additional contact with an illness suggestive of psittacosis. The virus of psittacosis was isolated from a sick parakeet in 1 of the aviaries concerned in the outbreak. The 2 patients involved in the outbreak recovered. Penicillin was administered to 1 while the other was treated symptomatically.

The apparent rarity of psittacosis as suggested by the paucity of reported cases indicates either low incidence or failure of recognition. Careful histories as to contact with psittacine or other birds capable of transmitting ornithosis, plus the use of the complement fixation test, will aid in the detection of cases.

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## EXPERIENCES WITH ANTIRETICULAR CYTOTOXIC SERUM (ACS) IN ARTHRITIS\*

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IN 1942 the representatives of the Academy of Sciences of the Ukrainian Soviet Socialist Republic passed a resolution that the therapeutic effect of the Bogomolets antireticular cytotoxic serum (ACS) was clearly established in the treatment of "rheumatism."<sup>3</sup> Sokolinski<sup>7</sup> considered rheumatic disease an allergic process involving active mesenchymal tissue and that ACS was indicated to restore the normal reactivity of connective tissue cells. He treated patients with "acute rheumatism" with ACS and reported that in most of the cases all rheumatic manifestations in the joints subsided within the 1st week. It was further reported by Strazhesko<sup>8</sup> that "In the case of rheumatism, the second period is hyperergic and a single injection of the serum in a stimulating dose stops the disease." Because of these very favorable statements regarding ACS in the treatment of rheumatism it was considered important that the further definition of its value be obtained.

**PREPARATION OF SERUM.** The antireticular cytotoxic serum† was prepared in rabbits according to the method of Marchuk.<sup>4</sup> It had a cytotoxin titer, determined by complement fixation of at least 1:100 and a hemolytic titer below 1:16. Dry lyophilized serum was dissolved in physiologic saline shortly before its use. No serum was injected after 10 days

standing in the liquid state, or if the solution became turbid. Frequent complement fixation tests were made to insure potency of the serum.

**EXPERIMENTAL OBSERVATIONS.** This research consists of 2 parts: (1) observations of the effect of ACS as a prophylactic and therapeutic agent against pleuropneumonia induced arthritis in rats and (2) clinical observation of ACS used to treat rheumatic disease especially chronic arthritis.

*Laboratory Animal Studies.* Arthritis was produced in rats by the injection of pleuropneumonia-like organisms. White rats, each weighing 100 gm., were inoculated intravenously. One group of animals served as untreated controls. Of a second group some rats were injected with normal rabbit serum while the test animals received potent homologous anti-rat ACS especially prepared for this study. In this group all serum injections were made before inoculation with pleuropneumonia-like organisms to test its prophylactic effect. A third group of rats received injections of ACS simultaneously with the inoculation of pleuropneumonia-like organisms and repeated serum injections on the 3rd and 6th day.

In Table 1 the fate of the rats inoculated with pleuropneumonia-like organisms otherwise untreated is shown. Three of the rats developed arthritis, 2 died of

\* Read at the Meeting of The New York Rheumatism Association, New York City, Nov. 22, 1946.

† Obtained through the kindness of Dr. Harry Goldblatt of Western Reserve University, Cleveland, Ohio.

pleuropneumonia and 1 remained well during the 3 weeks of observation. The dependability of pleuropneumonia-like organisms to produce arthritis in rats as previously demonstrated by the work of Sabin,<sup>6</sup> Preston *et al.*,<sup>5</sup> Collier<sup>2</sup> and others is thus corroborated.

The results of attempts to prevent the development of arthritis by injecting anti-reticular cytotoxic serum prior to inoculation with pleuropneumonia-like organisms are shown in Table 2. Doses ranged from 0.00005 to 0.00015 cc. Three injections

after infective pleuropneumonia-like organisms. Of the control group receiving normal rabbit serum, 3 animals developed arthritis, 1 pleuropneumonia and 2 animals died. In the group receiving ACS there was 1 case of arthritis, 4 deaths from pleuropneumonia and 1 rat remained normal. As used ACS was of no value as a therapeutic agent against the effects of pleuropneumonia infection.

CLINICAL INVESTIGATIONS. Observations were made on patients manifesting different stages of activity of rheumatoid

TABLE 1.—RESULTS IN 6 RATS OF INOCULATION OF PLEUROPNEUMONIA-LIKE ORGANISMS

Result	No. animals
Died of pleuropneumonia within 5 days . . . . .	2
Arthritis of joints of hind legs . . . . .	3
Well after 3 weeks . . . . .	1

TABLE 2.—RESULT IN RATS OF ACS NORMAL SERUM INJECTIONS GIVEN 9, 6 AND 2 DAYS PRIOR TO INOCULATION WITH PLEUROPNEUMONIA-LIKE ORGANISMS

Dosage (cc.)	Normal serum	ACS
0.00005 × 3 . . . . .	Died on 7th day	Died on 5th day
0.00005 × 3 . . . . .	Arthritis	Died on 5th day
0.0001 × 3 . . . . .	Died on 5th day	Died on 12th day
0.0001 × 3 . . . . .	Pleuropneumonia	Normal
0.00015 × 3 . . . . .	Died on 12th day	Arthritis
0.00015 × 3 . . . . .	Died on 12th day	Arthritis

TABLE 3.—RESULTS IN RATS OF ACS AND NORMAL SERUM INJECTIONS GIVEN SIMULTANEOUSLY WITH PLEUROPNEUMONIA-LIKE ORGANISMS

Dosage (cc.)	Normal serum	ACS
0.00005 × 3 . . . . .	Died on 7th day*	Normal
0.00005 × 3 . . . . .	Arthritis	Died on 5th day
0.0001 × 3 . . . . .	Arthritis	Died on 5th day*
0.0001 × 3 . . . . .	Died on 5th day*	Arthritis
0.00015 × 3 . . . . .	Arthritis	Died on 5th day*
0.00015 × 3 . . . . .	Pleuropneumonia	Died on 5th day*

\* Three injections planned; animal died after the second injection.

were given 9, 6 and 2 days before the introduction of the infective material. In the control group receiving normal rabbit serum, 4 of the rats died, 1 developed arthritis and 1 developed pleuropneumonia. In the group receiving potent ACS serum, 3 of the animals died, 2 developed arthritis and 1 remained normal. It appears from this study that with the technique used, ACS was of no value in preventing arthritis caused by pleuropneumonia-like organisms.

Table 3 shows the results of serum injection given simultaneously with and

arthritis and ankylosing spondylitis. At intervals of 3 or 4 days ACS was injected subcutaneously. The doses were originally 0.5, 1 and 1.5 cc.; later these doses were frequently reduced to 0.3, 0.6 and 0.9 or 1 cc. After intervals of 4 to 6 weeks many patients received a second series of injections, some a third series, and several a fourth series of injections similarly. No changes in other treatment previously administered, which often consisted of physical therapy and salicylates, were made except that 5 patients were hospitalized during treatment.

Twenty-nine patients were thus treated with ACS; 24 patients received 2 or more series of injections. Fourteen patients were injected in a similar manner with normal rabbit serum having no antireticular cytotoxic activity. In many instances it was not known until after evaluation of results whether the serum used was ACS or 'normal (control) serum. Some patients treated with ACS were at another time likewise injected with normal rabbit serum, also given as further control.

Changes in symptoms and physical signs were carefully noted before and after each series of injections; many patients were observed for 6 months or longer after treatment. The alleged stimulation of the connective tissue was followed. The dispersion of trypan blue injected intradermally, which Tatarinov<sup>9</sup> considered to be a dependable index of the activity of connective tissue as a physiologic system, was observed 90 times in 30 patients. A rapid spread of the dye was reported to indicate stimulation of the connective tissue. Although potent ACS was used, no consistent increase in the diffusion of intradermal trypan blue dye was noted. Furthermore the diffusion varies considerably depending upon the depth of injection which could not always be controlled. Because of these facts the reliability of this test was doubted, and so it was abandoned.

Other laboratory tests that have been suggested as indices of activity of the connective tissue are changes in (peripheral) blood morphology, especially an increase in monocytes and a decrease in the erythrocyte sedimentation rate. In all patients a total and differential white blood count and erythrocyte sedimentation rate were determined prior to and following each course of injections. In most cases there was no change in blood morphology. Of the 29 patients who received ACS, only 5 showed an increase in monocytes after injection. The increase exceeded 4% in only 1 instance—when a 7% monocytic response was observed 24 hours after injection of ACS during

the time this patient exhibited a moderate tissue inflammation at the site of injection accompanied by systemic fever of 100° F. The monocyte count subsequently fell to 1% and with further ACS treatment the number of monocytes remained at 2% of the total leukocyte count. The erythrocyte sedimentation rate gradually rose in 10 of the 29 patients treated; in 2 cases there was no change, in 17 patients there was a gradual fall in sedimentation rate during and after treatment.

**REACTIONS.** Inflammatory reactions at the site of injection were common. Forty-six per cent of the ACS-treated patients and 36% of the patients treated with normal rabbit serum manifested some degree of local reaction characterized by heat, swelling, tenderness and usually followed by pruritus. Most reactions occurred following the second or third injection. Inflammation usually started within 24 hours and disappeared within 72 hours. In 4 ACS treated patients systemic reactions evidenced by chills, fever, malaise and occasional axillary lymphadenopathy occurred. One patient developed generalized urticaria during the first series of injections. No systemic reactions occurred in the patients injected with normal serum. No relationship was noted between clinical improvement and the severity of reaction.

**CLINICAL RESULTS.** Table 4 summarizes the clinical evaluation of 29 patients treated with ACS and 14 patients injected with normal rabbit serum. Three patients who received ACS improved symptomatically. Three showed objective improvement; in 16 there was no change and 7 became worse. Of the control group (injected with normal rabbit serum) 1 individual improved symptomatically; 2 objectively; 7 revealed no change and 4 became worse.

**COMMENT.** Of the 3 patients showing definite objective improvement after injection of ACS, 1 presented a problem in diagnosis; differentiation between rheumatic fever and early rheumatoid arthritis could not be definitely made. The patient was 31 years of age; there was a history

of "rheumatic fever" 3 years previously when he had fever and inflammation of many extremity joints. The illness subsided spontaneously but recurred the following year. He had been treated with vaccines and Roentgen ray therapy to the spine for early spondylitis rhizomelique. There was roentgenologic evidence of sacroiliitis bilaterally. When first seen in the clinic, he stated that his knees had been swollen, painful and stiff for several weeks. The wrists, fingers and ankles had been stiff. Examination revealed that the patient had a temperature of 102° F. The knees were inflamed, tender and

white blood cell count fell to 6300 with 67% polymorphonuclears, 31% lymphocytes and 2% eosinophils. The trypan blue index remained 13. After 3 weeks a similar series of ACS injections were given. The patient felt so well that he neglected returning to the clinic. When seen 4 months later he stated that his joint pains and swelling had completely subsided 3 weeks after the last injection. On examination there was no evidence of joint disease. His sedimentation rate at this time was 10 mm. per hour, the leukocyte count was 7500 with 66% poly-

TABLE 4.—EVALUATION OF ACS AND NORMAL RABBIT SERUM USED IN TREATMENT OF PATIENTS WITH ARTHRITIS

	Symptomatic improvement	Objective improvement	No change	Worse
<i>Antirheumatic Cytotoxic Serum</i>				
Rheumatoid arthritis:				
Early . . . . .	1	1*	1	0
Mod. advanced . . . . .	0	0	5	3
Advanced . . . . .	0	1	6	2
Juvenile . . . . .	0	0	0	1
Spondylitis:				
Mod. advanced . . . . .	1	0	0	0
Advanced . . . . .	1	1	4	1
Totals (29 cases) . . . . .	3 (10.2%)	3 (10.2%)	16 (55%)	7 (24%)
<i>Control Rabbit Serum</i>				
Rheumatoid arthritis:				
Adult . . . . .	1	2	6	4
Juvenile . . . . .	0	0	1	0
Totals (14 cases) . . . . .	1 (7%)	2 (14%)	7 (50%)	4 (29%)

\* Diagnosis not certain—? rheumatic fever.

swollen with excessive synovial fluid. There was no loss of passive motion in the wrists, fingers or ankles although at the extremes of motion there was pain. Laboratory findings included erythrocyte sedimentation rate—39 mm. per hour (Westergren); white blood count 6900 with 76% polymorphonuclears, 22% lymphocytes and 2% eosinophils. The trypan blue index before ACS therapy was 13. The patient was treated with a series of 4 injections of ACS increasing from 0.25 to 1.25 cc. following which the joints were slightly more comfortable; there was little change objectively. The sedimentation rate rose to 42 mm. per hour; the

morphonuclear cells, 32% lymphocytes, 1% monocytes and 1% eosinophils.

The second patient, age 62 years, had had rheumatoid arthritis for 18 years. He had been treated in the clinic with physical therapy, gold salts, vaccines and high dosage vitamin D orally. He did not improve, so agreed to enter the hospital for further treatment. He was brought to the hospital in a wheel chair, unable to walk. There was advanced involvement of the knees, hips, spine, hands, shoulders and feet. The erythrocyte sedimentation rate was 136 mm. per hour. The patient was given a course of ACS injections ranging up to 2 cc. There were no local reac-

tions. Upon completion of this series there was a marked subjective and objective improvement, the joint synovitis subsided. The patient began to walk. The sedimentation rate reduced to 122 mm. per hour. A second course of injections of ACS was given 2 months later and a third 1 month after that. The patient continued to improve, joint inflammation lessened and there was increased range of motion. The sedimentation rate fell to 106 mm. per hour. Examination 1 year later revealed that the improvement was sustained.

The third patient was a man 27 years old with advanced ankylosing spondylitis of 8 years duration. He had received Roentgen therapy over the back and also had been treated with nicotinic acid. He came to the clinic requesting ACS therapy. Motion of the spine was greatly restricted and chest expansion was only  $1\frac{1}{8}$  inches. Forward bending while standing with the legs straight was so reduced that the fingertips were 24 inches from the floor. The erythrocyte sedimentation rate was 83 mm. per hour; leukocyte count 7400; there were 64% polymorphonuclear cells, 30% lymphocytes and 6% eosinophils. The first series of 3 ACS injections ranged from 0.5 to 1.5 cc. There was a marked tissue reaction at the site of injection accompanied by systemic fever of  $101.2^{\circ}$  F. following the last injection. A second series of injections was given 4 weeks later. There was no local reaction at this time. Five weeks later ACS was given in a third series of injections where again there was marked local reaction. From the beginning of the treatment the chest expansion increased from  $1\frac{1}{8}$  to  $1\frac{7}{8}$  inches and the finger to floor measurement improved from 24 to 14 inches. The erythrocyte sedimentation rate gradually fell to 39 mm. per hour. The patient stated he felt much stronger, had no back pain, was less handicapped getting in and out of an automobile and could carry a suitcase for the first time in many years. When reexamined 2 months later it was found that the improvement had been maintained. At this time the patient admitted that through-

out the course of ACS therapy he had been doing daily breathing exercises and calisthenics which he had overheard were advised to other patients.

Observation over a period of several months showed the symptomatic improvement experienced by 3 patients to be only temporary.

**Discussion.** Evaluation of any method of therapy for arthritis is difficult indeed. The natural changes in the course of the disease leading to improvement must always be considered. No effort was made in this study to evaluate the psychogenic factors which are known to influence the progress of rheumatoid arthritis. The improvement noted in the third case may be assumed to be due in part to exercises. The fact that objective improvement occurred in 2 patients of the control group suggests that benefit observed in the ACS treated cases may not be due to the antireticular cytotoxic characteristics of the serum but rather to a non-specific serum effect.

There have been relatively few studies of ACS used in the treatment of rheumatism. Bach<sup>1</sup> treated 48 cases, 32 hospitalized patients and 16 clinic patients. Besides rheumatoid arthritis the illnesses treated with ACS included rheumatic fever, gonorrheal arthritis, osteoarthritis and non-articular rheumatism. Clinical improvement was noted in 14 cases (29%); in 7 patients improvement was classified as "definite," in 7 others "slight." Benefit was mainly subjective and in many cases relapses occurred after a short time.

**Conclusions.** 1. Polyarthritis induced in rats by pleuropneumonia-like organisms was not affected in time of onset or severity by the use of antireticular cytotoxic serum either prophylactically or therapeutically.

2. With the method of administration used in this study ACS therapy was of no benefit in the great majority of patients with rheumatoid arthritis. In the few cases apparently improved, benefit was usually transient. There was no dependable effect of ACS on the clinical course of rheumatoid arthritis.

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## GLYCOGEN STORAGE (VON GIERKE'S) DISEASE PREDOMINANTLY INVOLVING THE HEART

### REPORT OF A CASE WITH HISTOCHEMICAL PHOSPHATASE STUDIES

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ENLARGEMENT of the heart due to abnormal glycogen storage is of rare occurrence. The present communication deals with a case in which large amounts of glycogen were demonstrated in the heart and other organs by several histochemical methods. In addition, the distribution of alkaline and acid phosphatase in sections of various organs was investigated. Such a study seemed of particular interest in view of the findings of Thannhauser, Sorkin and Boncoddio.<sup>36</sup> These authors reported on chemical examinations a marked decrease in alkaline phosphatase activity in the livers of 3 patients who died of the hepatic form of von Gierke's disease.

**Case Abstracts.** The patient was a female child of Polish-Russian extraction. There was no consanguinity between the parents. The mother had given birth to 3 children, at the age of 19, 20 and 22. These 3 children are healthy and developing well. At the age of 25 this female child to be reported was born. The delivery was without difficulty. The infant did not take food well and did not gain weight. It also had frequent loose, foul smelling bowel movements. At the age of 6 weeks the child was admitted to the Elizabeth A. Horton Memorial Hospital in Middletown, N. Y., under the care of Dr. A. Romain. Physical examination revealed a poorly nourished, dehydrated baby weighing 3910 gm. The temperature was normal. The blood count was essentially normal. Several urine examinations revealed absence of sugar and acetone. Upon treatment with saline infusions, and pectin agar, the baby gained 430 gm. in 9 days. The child appeared to be markedly improved upon discharge. At home she failed, however, to gain further weight and did very poorly. Four weeks later the mother noticed in the morning that the child was cyanotic and dyspneic. It

was dead upon admission to the hospital a few hours later. An autopsy was carried out 20 hours after death.

**NECROPSY.** The general appearance of the body was that of a 10 weeks old female baby in a very poor nutritional state. The skin was dry and the eyes sunken in. No edema or jaundice was noticed.

The abdominal cavity did not contain any free fluid. The liver was one finger beneath the costal margin. In the right pleural cavity a few cc. of free fluid was found. The heart was very considerably enlarged and weighed 99 gm. (normal 23 gm.)<sup>7</sup> (Fig. 1.) The pericardial sac did not contain any increased amount of free fluid. The pericardium was smooth. Dissection of the heart showed no congenital abnormalities. The foramen ovale was closed. There was marked hypertrophy of the ventricles, the left measuring up to 2 cm. and the right up to 0.7 cm. in thickness. The myocardium, on cut section, had a grayish, pale color. The papillary muscles were very markedly hypertrophied. The endocardium was smooth and pale. The aorta and coronary arteries appeared normal. The lungs weighed 130 gm. The right upper and portions of the middle and lower lobe were hypo-aerated and dark red in color. The left lung contained small patchy areas of hypo-aeration. The mucosa of the bronchi was pale.

The liver was moderately enlarged and weighed 220 gm. (normal 140 gm.)<sup>7</sup> The outer surface was smooth and brownish. The section oozed a good amount of dark red blood and had a fairly uniform reddish appearance. The spleen was not enlarged and weighed 15 gm. On cut section it was purplish and showed the anatomical markings well. The adrenals appeared to be somewhat atrophic. Thymus and pancreas were not unusual on gross examination.

The kidneys were not enlarged, each



weighing 20 gm. On cut section they appeared normal. The remaining organs of the G. U. tract and of the G. I. tract appeared grossly normal. Sections through lumbar vertebrae showed moist red bone marrow. The brain appeared grossly normal.

**MICROSCOPIC EXAMINATION:** Tissues were fixed in 20% formalin and sections stained with hematoxylin-eosin. Pieces from heart, adrenals, kidneys and liver were in addition fixed in absolute alcohol and in cold acetone. Glycogen was demonstrated with Best's carmine stain and the Bauer-Feulgen stain,<sup>4</sup> as well as by Gomori's modification of Bauer's technique.<sup>17</sup>

Kabat and Newman.<sup>43</sup> The incubation time varied from 4 to 48 hours. No counterstain was employed. Lipase activity was demonstrated with Gomori's stain<sup>16</sup> with some modifications.<sup>41</sup>

**Heart.** Sections through many areas of the heart stained with hematoxylin-eosin appear similar throughout (Fig. 2). The muscle fibers are hypertrophied and reveal vacuolization. In many muscle fibers these vacuoles appear as large empty spaces. On cross-section these empty spaces are surrounded by a narrow ring of pink staining sarcoplasm. The nuclei are mostly situated at the periphery. Occasionally they appear



FIG. 1.—The left ventricle of the heart is opened. Hypertrophy of the wall and papillary muscles is conspicuous.

Satisfactory staining for glycogen was possible not only in alcohol and acetone fixed tissue but also after fixation in 20% formalin.<sup>3</sup>

Alkaline phosphatase was demonstrated with Gomori's technique<sup>12</sup> in the modification of Kabat and Furth.<sup>20</sup> The slides were incubated for 12 to 14 hours in the substrate mixture. No counterstain was used. Acid phosphatase activity was revealed with Gomori's technique<sup>12</sup> as modified by Wolf,

to be in the center. Glycogen stains reveal the intracellular spaces in the muscle fibers to be filled by fine and coarse granules and rods (Fig. 3). Occasional glycogen granules appear to be lying outside the muscle fibers. No glycogen is present in the nuclei.

**Alkaline Phosphatase:** There is slight activity in the nuclei of muscle fibers and faint in the remaining remnants of the sarcoplasm. The capillaries and small arteries show very marked phosphatase activity.

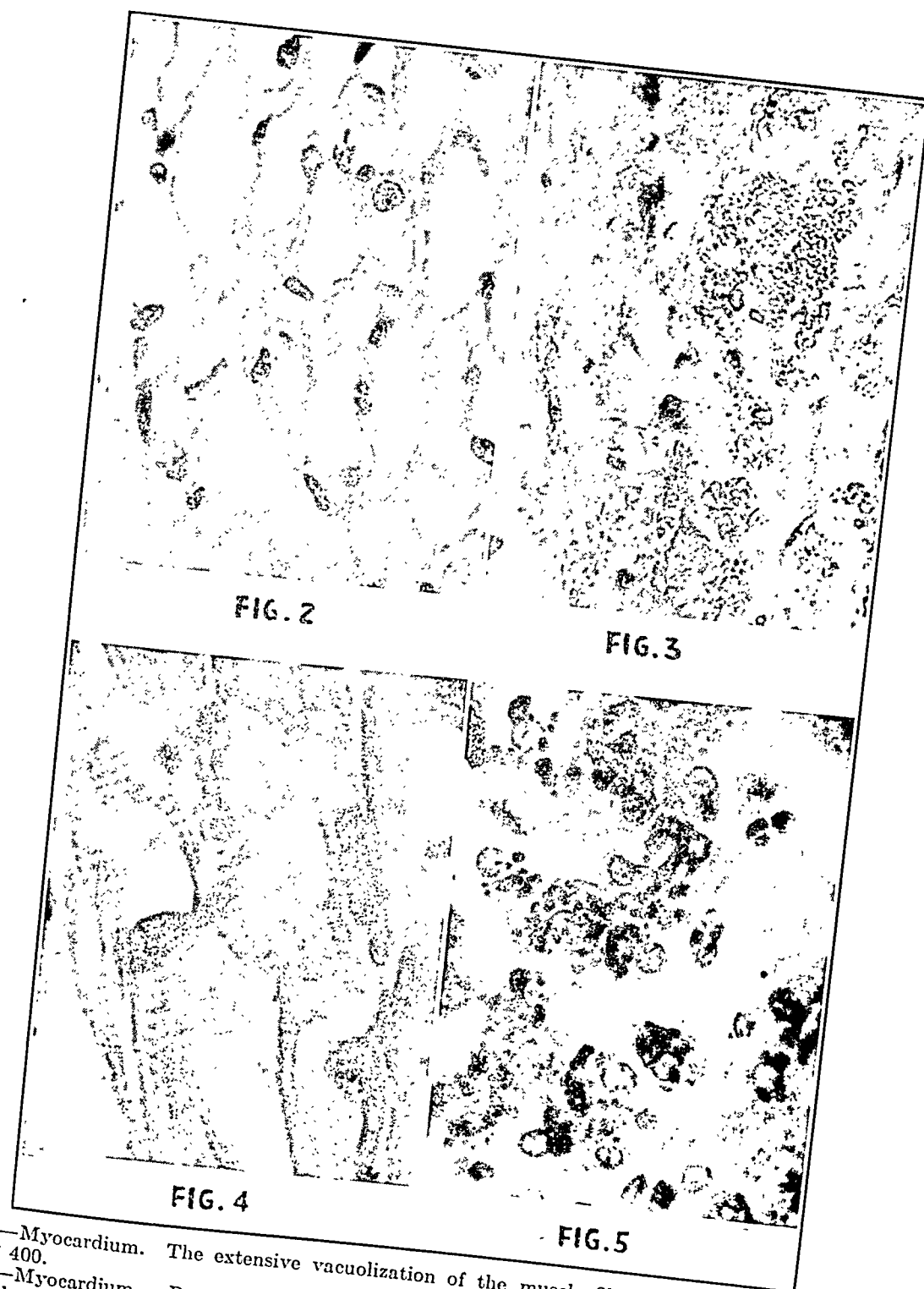


FIG. 2

FIG. 3

FIG. 4

FIG. 5

Fig. 2.—Myocardium. The extensive vacuolization of the muscle fibers is seen. Hematoxylin-eosin.  $\times 400$ .  
 Fig. 3.—Myocardium. Best's carmin stain for glycogen. The droplets filling the muscle fibers correspond to the red staining. Glycogen.  $\times 400$ .  
 Fig. 4.—A section of myocardium stained for acid phosphatase. The sites of enzymatic activity stained dark. Nuclei and cross-striations show enzymatic activity.  $\times 900$ .  
 Fig. 5.—Liver. Bauer-Feulgen stain for glycogen. The dark droplets filling the liver cells represent glycogen. Several Kupfer cells located in the dilated sinusoids are loaded with glycogen.  $\times 540$ .

*Acid Phosphatase* (48 hours incubation): There is distinct phosphatase activity in muscle fibers not occupied by glycogen. The striations are very prominent (Fig. 4). There is considerable activity in the nuclei of the muscle fibers as well as of those in the connective tissue and vessel walls.

*Lungs.* Section through grossly changed areas show considerable thickening of alveolar septa due to infiltration by mononuclear cells as well as occasional polymorphonuclear leukocytes. In addition considerable congestion of capillaries is present. There is exudate found in many alveolar spaces composed of large alveolar cells, smaller mononuclear cells, and occasional polymorphonuclear leukocytes. Glycogen is demonstrable in the smaller bronchi in the epithelium, smooth muscle cells and within the cells of cartilage. Many of the large alveolar cells contain glycogen granules.

*Liver.* Hematoxylin-eosin stained sections show the liver cells large and vacuolated. The cell nuclei mostly occupy a central position. The sinusoids are markedly congested and occasional Küpffer cells are swollen and detached from the wall. Sudan stain on frozen section reveals only a very moderate amount of fat droplets in most liver cells. Glycogen stains demonstrate large amounts of glycogen in the liver cells. The glycogen forms small and coarse granules and rods. Many of the Küpffer cells contain considerable amounts of glycogen (Fig. 5).

*Alkaline Phosphatase:* Nuclei, chromatin and nuclear membranes show a fair amount of alkaline phosphatase while the cytoplasm contains only very little. The activity of the sinusoidal endothelium varies in different fields. Bile capillaries are not stained (Fig. 6).

*Acid Phosphatase* (4 hours incubation): Considerable activity in nuclei and cytoplasm is seen (Fig. 7). Prominent staining is also apparent in the nuclei of bile ducts and in the nuclei located in the vessel walls. The Küpffer cells exhibit acid phosphatase activity. When the incubation period was extended to 24 hours complete darkening of the section occurred obscuring all cellular details.

*Lipase Activity* (48 hours incubation): Considerable lipase activity is present, localized exclusively in the cytoplasm of the liver cell cords.

*Kidney.* No significant changes are seen in sections stained with hematoxylin-eosin. Glycogen stains, however, reveal a considerable amount of glycogen in the distal convoluted tubules, Henle's loops and collecting tubules. The proximal convoluted tubules are apparently free. Some glycogen is also present in the glomerular epithelium (Fig. 8).

*Alkaline Phosphatase:* Conspicuous phosphatase activity is seen in the cytoplasm of the proximal convoluted tubules. It is most prominent at the brush borders. All other tubules show phosphatase activity only in the nuclei. Similarly the nuclei in the glomeruli show phosphatase activity. Some small arteries in the cortex as well as capillaries in the medulla are in addition the site of distinct enzymatic activity (Fig. 9).

*Acid Phosphatase* (48 hours incubation): There is cytoplasmic phosphatase activity in most of the tubules located in the cortical portion of the kidney. In addition the glomeruli are distinctly positive. In the medulla only the nuclei of the tubules show phosphatase activity. While after a 4 hour incubation period practically no staining is seen, slides incubated 24 hours show similar, although less marked staining as slides after 48 hours incubation.

*Adrenals.* Hematoxylin-eosin stained sections show considerable congestion of the medulla. Glycogen stains reveal a good amount of glycogen in the cortical cells and large amounts in the cells of the medulla. Occasional glycogen granules are present in the periadrenal fat tissue.

*Alkaline Phosphatase:* There is considerable amount of phosphatase activity in the nuclei and cytoplasm of the cortical cells. The zona glomerulosa stains less intensely than the zona fasciculata and reticularis. The medullary cells contain a fair amount of alkaline phosphatase (Fig. 10).

*Acid Phosphatase* (4 hours incubation): Considerable activity is seen in the cortex and medulla (Fig. 11). In sections stained for a longer time the intense staining reaction obscures all cellular detail.

*Pancreas.* The Langerhans islands are numerous and some of them very large. In sections stained with Best's carmin, the Langerhans islands are outlined as red areas due to the large amount of glycogen which they contain. In contrast the acinar cells contain only traces. Large amounts of gly-



FIG. 6

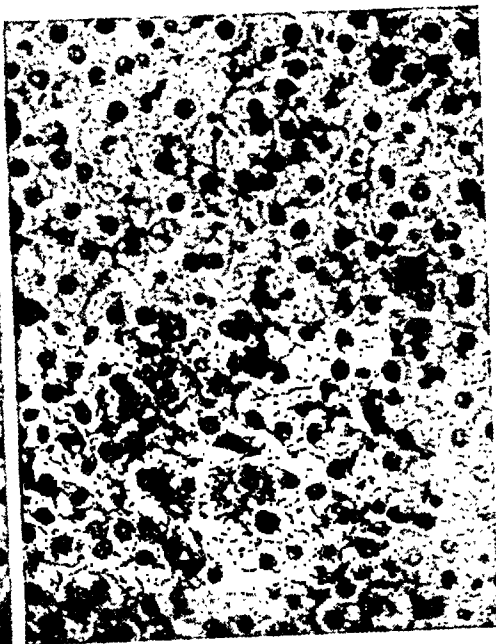


FIG. 7

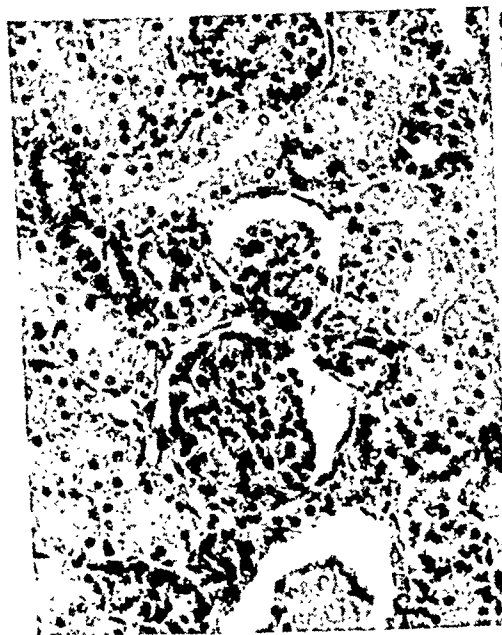


FIG. 8



FIG. 9

FIG. 6.—A section of liver stained for alkaline phosphatase. The sites of enzymatic activity stain dark. Nuclei and sinusoids are stained while the cytoplasm shows only little staining.  $\times 300$ .

FIG. 7.—A section of liver stained for acid phosphatase. The sites of enzymatic activity stain dark. Nuclei and cytoplasm of liver cells reveal acid phosphatase activity.  $\times 300$ .

FIG. 8.—Kidney. Best's carmin stain for glycogen. Glycogen granules are present in the capsular epithelium of the glomeruli and in distal convoluted tubules.  $\times 400$ .

FIG. 9.—A section of kidney stained for alkaline phosphatase activity. The sites of enzymatic activity stain dark. Alkaline phosphatase is present in the proximal convoluted tubules.  $\times 30$ .

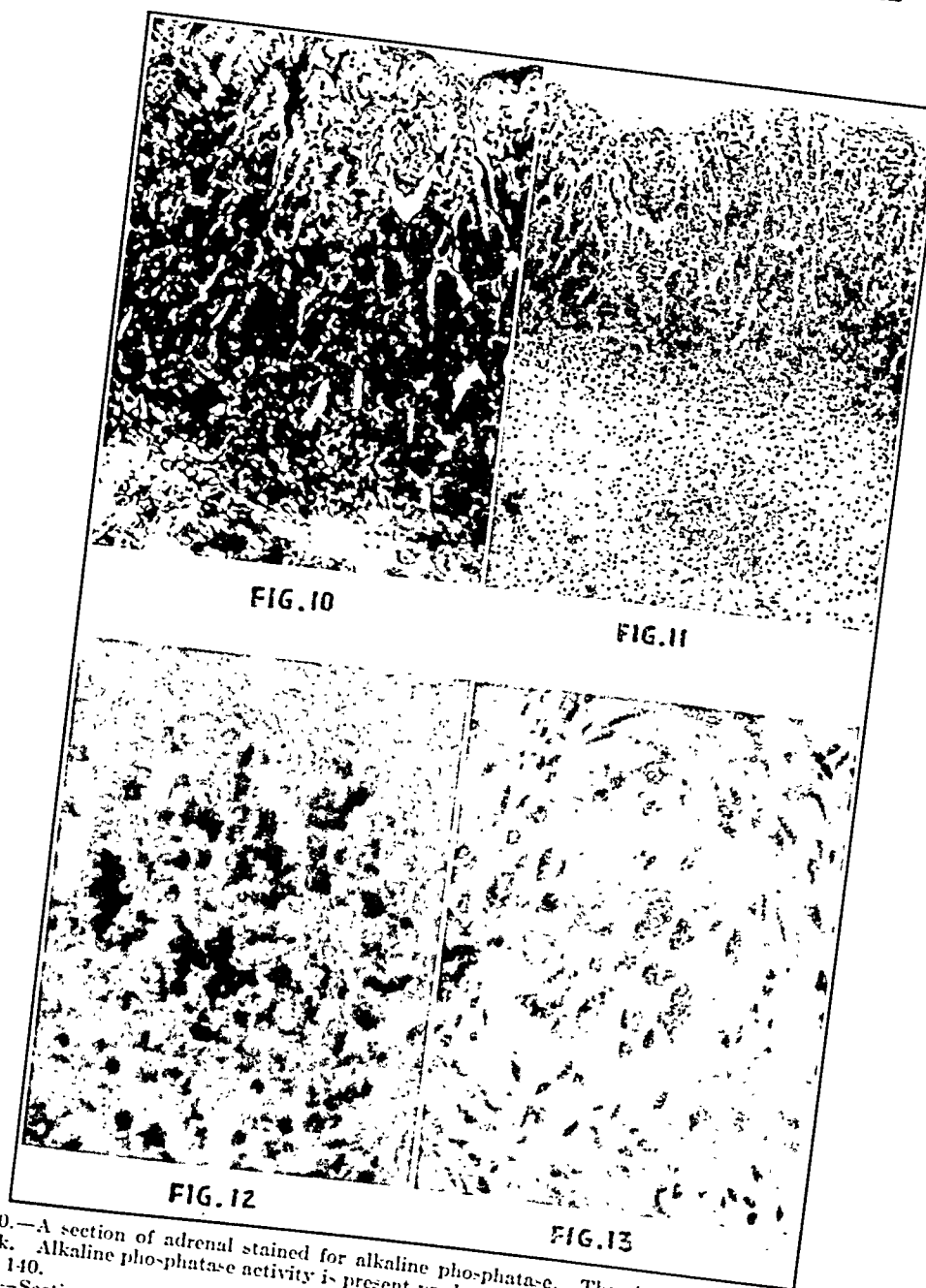


FIG. 10

FIG. 11

FIG. 12

FIG. 13

FIG. 10.—A section of adrenal stained for alkaline phosphatase. The sites of enzymatic activity stain dark. Alkaline phosphatase activity is present predominantly in the zona fasciculata and reticularis.  $\times 140$ .

FIG. 11.—Section of adrenal stained for acid phosphatase. The sites of enzymatic activity stain dark. Acid phosphatase is present in the cells of the cortex and medulla.  $\times 100$ .

FIG. 12.—An enlarged Langerhans islet of the pancreas. The dark granules in many of the cells correspond to the blue stain.  $\times 450$ .

FIG. 13.—Myenteric plexus in the large intestine. Best's carmalum stain for glycogen. The granules in the nerve cells represent glycogen.  $\times 300$ .

cogen are also present in the cells of the larger ducts. In sections stained with the Gomori chromium hematoxylin-phloxin stain,<sup>13</sup> the majority of the cells in the Langerhans islands stain blue and therefore represent beta cells (Fig. 12).

*Spleen.* In contrast to the lymphocytes some of the large mononuclear cells contain glycogen.

*Lymph Nodes and Thymus.* Occasional reticulo-endothelial cells contain glycogen granules, while the lymphocytes are devoid of them.

*Intestine.* Smooth muscle cells contain a large amount of stainable glycogen. In sections stained with Best's carmin, the muscularis mucosa stands out as a red colored band. The nerve cells of the myenteric plexus of Auerbach contain large amounts of glycogen (Fig. 13).

*Diaphragm.* In sections stained with hematoxylin-eosin most of the muscle fibers appear normal, while occasional ones have a somewhat vacuolated appearance. Specific stains reveal that these vacuoles are due to glycogen infiltration. The other muscle fibers contain occasional small glycogen granules.

*Brain.* Many cells in various sections from the brain contain glycogen in forms of fine cytoplasmic granules. The glia cells appear to be more involved than the ganglion cells.

*Blood-vessels.* In all organs many of the blood-vessels contain glycogen. It is found in the muscle fibers as well as in the endothelial cells.

**Discussion.** In glycogen storage disease there exists apparently a developmental defect involving the enzyme systems necessary for the transformation of glycogen to dextrose and of dextrose to glycogen. The various metabolic aspects of this disease have been recently discussed by Mason and Anderson,<sup>25</sup> Kato,<sup>21</sup> and Bridge and Holt.<sup>6</sup>

While in the more common form of Von Gierke's disease, the liver and often the kidneys are the main site of glycogen storage, in some of the cases the heart is the site of grossly abnormal glycogen deposition. Review of the literature reveals 17 cases in which the presence of grossly abnormal amounts of glycogen was demonstrated in the heart muscle

without other congenital abnormalities either by histochemical methods or chemical analysis (Sprague, Bland and White,<sup>35</sup> later proven as a typical case;<sup>19</sup> Pompe, 3 cases;<sup>30</sup> Putschar;<sup>32</sup> Humphreys and Kato, 3 cases;<sup>19</sup> Antopol, Heilbrunn and Tuchman;<sup>2</sup> Hertz and Jeckeln;<sup>18</sup> Wolff;<sup>44</sup> Mutgeert;<sup>27</sup> Gardner and Simpson;<sup>10</sup> van Greveld;<sup>37</sup> Antopol, Boas, Levinson and Tuchman;<sup>1</sup> Bonaba, Saldun de Rodriguez and Ferreira Beruti;<sup>5</sup> Scheidegger;<sup>33</sup> and Schneider.<sup>34</sup>)

In addition, in these patients the liver showed also a varying degree of grossly demonstrable enlargement. Kimmelstiel's case occupies probably an intermediate position.<sup>22</sup> In this case the liver was enormously enlarged due to deposition of glycogen, while the heart muscle revealed glycogen infiltration on microscopic examination without being distinctly hypertrophic. Most of the children with the cardiac form of glycogen disease died before reaching the 1st birthday. Only 2 patients were reported which attained an age of 11 and 15 years respectively.<sup>1,10</sup>

In the present case glycogen was found not only in the heart and liver but also in many other locations on microscopic examination. This is in full accord with the cases reported in the literature in which a varying amount of glycogen infiltration in different organs occurred. While most investigators employed Best's carmin stain for the demonstration of glycogen under the microscope, use was made in addition of the Bauer technique in its original form and as modified by Gomori. As Gomori<sup>17</sup> has pointed out, these methods constitute a more specific staining reaction based on known chemical principles than the purely empirical Best's stain.

In the liver not only the hepatic cells proper but also the K pffer cells showed large amounts of glycogen. Cells belonging to the reticulo-endothelial system in lymph nodes, spleen and thymus also contained glycogen, although less regularly. Only in the case of Wolff<sup>44</sup> were appreciable amounts of glycogen found in K pffer cells and reticulo-endothelial elements of the spleen. In all other reports in which

mention is made of the Kupffer cells they were found either to be devoid of glycogen or contained only occasional traces. While, therefore, the reticulo-endothelial system and particularly the Kupffer cells do not often participate in the glycogen storage, the present case as well as Wolff's report do not permit the conclusion that in contrast to Gaucher's and Pick-Niemann's disease the reticulo-endothelial system in von Gierke's disease is not involved by the abnormal cell metabolism.<sup>2,24</sup>

No regular distribution within the tubular segments is seen in the kidneys of cases with glycogen disease. This has been pointed out by Wolff<sup>14</sup> and von Gierke.<sup>39</sup> In contrast, in the diabetic kidney the glycogen is found in the terminal segment of the proximal convoluted tubules and to a lesser degree in the ascending limbs of Henle's loop.<sup>25</sup> With the maceration and dissection technique, Oliver found no localization to any particular part of the nephron in von Gierke's disease, for collections of glycogen containing cells are scattered irregularly throughout all its parts.<sup>29</sup>

Glycogen deposition in the brain has been described in several instances.<sup>22,33,34</sup> In the present case in addition cells in the nervous plexus of the intestinal tract participated in the abnormal storage. In cases of amaurotic family idiocy (Tay-Sachs disease) Globus<sup>11</sup> found abnormal lipoid material not only in the central nervous system but also in the nerve cells of the abdominal viscera, including the gastro-intestinal tract.

with von Gierke's disease with muscle and liver phosphorylase preparations, observed only little breakdown of the stable glycogen.

The changes noticed in the pancreas deserve some comment. While in a number of reports no mention is made of the pancreas, no significant changes were recorded by Humphreys and Kato, in 3 cases of the cardiomegalic type<sup>19</sup> and by Hertz and Jeckeln<sup>15</sup> and Antopol and co-workers<sup>1</sup> in another case of this type. Von Gierke stressed the absence of changes in the Langerhans islands in 2 cases of the hepatomegalic type.<sup>38,40</sup> On the other hand, in 2 cases of the atter type described by Krakauer<sup>23</sup> and in a similar case reported by Esser and Scheidegger<sup>5</sup> the islands were found to be large and abundant. Similarly enlarged islands were seen in the case of the cardiomegalic type observed by Scheidegger<sup>3</sup> and Schneider<sup>21</sup> and in the case of Kimmelstiel.<sup>22</sup> Faber in a case of the hepatomegalic type found the number of islands diminished and some very large.<sup>9</sup>

The significance of the hyperplastic changes in the islands of Langerhans is difficult to evaluate. Changes of this kind are found in newborn babies from mothers with diabetes<sup>21</sup> and those who develop signs of diabetes mellitus later<sup>22</sup> as well. It is also sometimes found in infants suffering from erythroblastosis.<sup>21</sup> However, hyperplasia of the Langerhans islands occurs occasionally in infants without

In view of the fact that hyperplasia of the Langerhans islands appears to occur fairly frequently in glycogen storage disease, one might speculate as to a possible connection with increased demand for insulin.

Ingestion of carbohydrates provokes in many patients with von Gierke's disease an abnormally high and persistent rise of blood sugar. It is possible that the hyperplasia of beta cells indicates increased insulin production called upon to depress the increased amount of the sugar in circulation.

**Summary.** The 18th proven case of von Gierke's disease with marked enlargement of the heart is described. On microscopic examination glycogen storage was demonstrable in the cells of various organs, including the brain, the nerve cells in the myenteric plexus of the intestinal tract and the Küpffer cells of the liver. The histochemical distribution of alkaline and acid phosphatase in liver, kidney, adrenal and heart was found to be normal. Marked hyperplasia of the Langerhans islands in the pancreas with preponderance of beta cells was present. The significance of these findings is discussed.

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## STUDIES OF CRYOGLOBULINS

## I. UNUSUAL PURPURA ASSOCIATED WITH THE PRESENCE OF A HIGH CONCENTRATION OF CRYOGLOBULIN (COLD PRECIPITABLE SERUM GLOBULIN)\*

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THE literature contains but sparse reference to cases of purpura associated with cold precipitable serum globulins. There are only 9 reports of proteins precipitating spontaneously from serum (usually cooled).<sup>2,3,4,6,9,11,12,15,17</sup> Purpura was observed in 2 of these cases.<sup>15,17</sup>

There are 3 reports on the association of purpura and hyperglobulinemia.<sup>1,10,14</sup> In 1 of the papers,<sup>10</sup> a viscous serum protein is reported.

The purpose of the present paper is to report an unusual case and discuss some of its implications. The chemical characteristics of the protein observed in this case have been described in detail elsewhere.<sup>7</sup>

pin-point flat rash on his ankles. "Red blisters" formed, which later turned black and finally fell off, leaving a pigmented area. He began to notice that he was very sensitive to cold. A cold wind or exposure to cold of any sort produced pain and swelling in the exposed parts. It was necessary for him to wear heavy underwear and an unusual amount of clothing to keep warm.

He experienced another attack of sharp pain across the epigastrium in April 1937. This lasted for about 1 week and was similar to the first one. Again there was no jaundice.

In 1937 the purpuric skin lesions extended up to and included the knees. The lesions remained unchanged until 1939. At this time they began to spread again and involved the ears, thighs, abdomen, buttocks and scrotum. He was not able to secure any adequate medical explanation for these

5 years younger has an enlarged heart and prostate. One sister is a diabetic.

The patient was happily married since 1917 and had 3 children, all living and well. Until 1934 he was a broom manufacturer and real estate agent. In 1934 he began working in a hard-rock mine in Montana, where he was exposed to ore containing lead, zinc, copper, silver, gold, bismuth, arsenic and sulfur.

On physical examination in July 1942, the blood pressure was found to be 108/72. The pulse and temperature were normal. There was marked narrowing and sclerosis of the retinal arterioles, but there were no retinal hemorrhages. Examination of the lower extremities revealed extensive subcutaneous hemorrhages of various age, the majority being old. He had edema of the feet and ankles. There was considerable brownish pigmentation of the skin of the lower legs. The purpuric lesions were also present on the ears, abdomen, buttocks and scrotum.

The laboratory findings in July 1942 were as follows: Urinalysis and serologic tests for syphilis were negative. The hemoglobin was 13.8 gm. %. The blood platelets were 118,000, 201,000 and 196,000 per c.mm. on 3 successive occasions. Blood smears were negative. The bleeding time, clotting time, clot retraction and prothrombin time were well within normal limits. The blood urea nitrogen was 32 mg. per 100 cc. Fasting blood sugar, cholesterol, phosphatase, ascorbic acid, serum bilirubin, calcium and phosphorus were all within normal limits. The basal metabolic rate was -5. The brom-sulfalein liver function test showed a "Grade 1" dye retention. Gastric analysis revealed a total acidity of 48 units with free hydrochloric acid of 30 units; the total quantity was 150 cc. A chest Roentgen ray film was negative.

The diagnosis in 1942 was "cold allergy." The patient was desensitized to histamine phosphate and given vitamin P, but without apparent relief.

About 4 months later, on Dec. 1, 1942, he was admitted to the University of Minnesota Hospital. He complained of severe pain in the left lower chest, accompanied by dyspnea, cough, blood-streaked sputum and fever. These symptoms were noted first about 2 months previously. He had had severe attacks of precordial oppression and dyspnea on November 3, 13 and 30. After that

time, he had precordial distress upon exertion. The purpuric lesions on the extremities were increasing.

In December 1942 the blood pressure had increased to 156/94. The temperature was 98.4°, pulse 90 and respiration 20. There was slight dullness, diminished breath sounds and diminished tactile fremitus at the base of the left lung posteriorly. The heart was slightly enlarged to the left, cardiac rhythm was regular and no murmurs were heard. The liver was palpable 2 cm. below the right costal margin in the mid-clavicular line. There was a slight pitting pretibial edema. A finely mottled brown pigmentation was noted on the ears, hands, wrists, feet, legs, thighs and about the waist. There were fresh petechiae on both legs.

Urinalysis revealed a 1+ to 2+ albumin with an occasional leukocyte. The hemoglobin was 11.2 gm. per 100 cc. of blood. The leukocyte count was 10,900, 64% neutrophils, 26% lymphocytes, 1% basophils and 9% eosinophils. Serologic tests for syphilis were negative. The blood urea nitrogen was 25 mg. %. There was only a trace of serum ascorbic acid. The prothrombin time and coagulation time were normal. Bleeding time was 7.5 minutes. The cuff test was positive. The platelet count was 165,000 per c.mm. Sedimentation rate was 36 mm. in 1 hour (Westergren method). The vital capacity was 2000 cc., and the venous pressure was 13.5 cm. of water.

A chest Roentgen ray revealed generalized cardiac enlargement, a tortuous aorta, bilateral congestion of the lungs, and a small amount of fluid in the left pleural cavity. A roentgenkymogram showed no evidence of myocardial infarction. Electrocardiographic studies revealed a pattern suggesting left ventricular strain. A biopsy of the skin showed what was interpreted as a "capillaritis." This consisted of moderate round cell infiltration about the capillaries in the purpuric areas. A deltoid muscle biopsy gave negative findings.

The patient was confined to bed and given 100 mg. of vitamin C twice daily. It was found that he was sensitive to moccasin snake venom, and attempts made to desensitize him were without benefit. His cardiac condition gradually improved, and the venous pressure fell to 7.5 cm. of water. He was discharged on Jan. 30, 1943, and advised to take 500 mg. of hesperidin 4 times daily.



The term *cryoglobulin* is thus suggested to represent a group of *proteins* with the common property of precipitating (or gelifying) from cooled serum. This is similar to the use of the term Bence-Jones proteins to represent a *group* of proteins precipitating at 60° C. The cryoglobulins may precipitate at room temperature if they occur in high concentration.

With respect to solubility, ultraviolet absorption spectrum and nitrogen content the protein from the serum of the case we described resembles the  $\gamma$  globulins. However, this protein, unlike the  $\gamma$  globulins, is soluble in water but insoluble in dilute salt solutions. So far as could be determined,<sup>7</sup> the molecular weight and viscosity are greater than those of the  $\gamma$  globulins.

precipitates in the capillaries of those areas where the temperature falls significantly below 37° C.

**Discussion.** As mentioned previously the literature contains but 9 reports of proteins precipitating spontaneously from serum. There are 3 additional references on the association of unusual serum proteins and symptoms similar to those presented by the present case. A brief description of these cases is given in Table 1.†

The cases of Waldenström<sup>13</sup> and Shapiro *et al.*<sup>10</sup> did not show any cold-precipitable proteins and the globulins responsible for the hyperglobulinemia should therefore not be called cryoglobulins. The purpura in these cases, however, may have been



FIG. 1.—Photomicrograph of renal biopsy from Case J. P., to show the extent of the chronic glomerulonephritis on Nov. 24, 1943; hematoxylin and eosin,  $\times 90$ .

In 0.9% saline at body temperature this protein is very soluble but at room temperature it is almost completely insoluble.\* It seems possible that the acropurpura and marked sensitivity to cold could be due to stasis secondary to increased viscosity, or it is even possible that the cryoglobulin

due to stasis in the peripheral capillaries on the basis of increased blood viscosity or rouleaux formation as a result of the hyperglobulinemia.<sup>5,8</sup> Anderson and Samuelson<sup>1</sup> did not report whether or not the serum from their patient contained any cold-precipitable proteins. All of the other

\* The solubility measurements were made at pH 5.7, the isoionic point of the protein. It is likely that the protein would be more soluble at the pH of blood.

† A case of periarteritis nodosa with cryoglobulinemia and some clinical findings similar to the case described here has recently been reported by B. Shapiro and E. Wertheimer (Brit. J. Exp. Path., 27, 225, 1946).

reports included in Table 1 specified proteins which precipitated on cooling.

Waldenström speculates that his patients with purpura and hyperglobulinemia may have chronic virus disease.<sup>13,16</sup> He believes that the mechanism of the increased globulin formation is analogous to the predominant formation of virus protein in a plant infected with tobacco mosaic virus. It seems more logical to

abnormal serum globulins, especially cryoglobulins. Thus "purpura cryoglobulinemica" may be recognized as a sub-group of Waldenström's "purpura hyperglobulinemica," the former being a more qualitative and the latter a more quantitative designation.

The site of formation of cryoglobulins is unknown, but there are 2 indications that they may be produced in the liver. As

TABLE 1.—CASES SIMILAR TO THE PRESENT INSTANCE EITHER WITH RESPECT TO UNUSUAL SERUM PROTEINS, SYMPTOMATOLOGY, OR BOTH

Observer	Diagnosis	Some of the signs and symptoms	Protein ppt. conc. (gm. %)
Wintrobe and Buell	Multiple myeloma (previously diagnosed as Raynaud's disease)	Cold sensitivity, blanching of skin, peculiar mottling of extremities, nose bleeds, oozing of blood from tongue and gums, thromboses of retinal veins	7.25 (plasma)
Schumacher, Williams and Coltrin	Multiple myeloma	Epistaxis, rectal and vaginal hemorrhage; serum protein "coagulated on exposure to air"	
von Bonsdorff, Groth and Packalen	Multiple myeloma	Bleeding of gums on slight pressure, slight retinal bleeding, congestive heart failure	
Bing	Multiple myeloma	(No information available)	
Holmberg and Gronwall	Chronic rheumatic infectious arthritis and spondylitis	(No information available)	1.3 (plasma)
Stein and Wertheimer	Kala-azar (dogs and humans)	(No information available)	0-1.4 (serum)
Atlas, Corden and Bunata	"Liver disease"	(No information available)	
Shapiro, Ross and Moore	Multiple myeloma	Oozing of blood from gums, occasional grossly bloody urine, numerous purpuric spots, occasional vaginal staining	4.2 (serum)
Waldenström	"Incipient myelomatosis or essential hyperproteinemia"	Joint pain, nose bleeds and hyperglobulinemia	
Waldenström	"Purpura hyperglobulinemica"	Chronic purpura of extremities and hyperglobulinemia (3 cases)	
Anderson and Samuelson	(No diagnosis established)	Blue-violet discoloration of hands, feet, nose and ears; "multiple septic emboli and thrombi of retina;" joint pains; hyperglobulinemia	
Flemberg and Lehmann	(No diagnosis established)	Sensitivity to cold, purpura beginning on legs, arms and face which gradually became severe	1.3 (serum)
Lerner and Watson	Cryoglobulinemia and cardiovascular renal disease	Extensive acro purpura, oozing of blood from gums and nose, congestive heart failure	0.8 (serum)

assume, however, that cryoglobulin formation may be the result of any one of several etiologic agents, *c. g.*, infection (virus and bacteria), malignancy, hepatic cirrhosis, etc.

The reports which are summarized in Table 1 emphasize the association of purpura, or hemorrhagic tendency, with

will be noted in Paper II which follows: small amounts of cryoglobulins appear in some cases of congestive heart failure with enlarged livers. Second, it has recently been noted that the cirrhotic livers of mice poisoned with carbon tetrachloride contain cold precipitable proteins.\*

\* N. Kretchmer (to be published).

It is of interest to note that the muscle protein, myosin, has solubility properties<sup>12</sup> similar to the cryoglobulin in the serum of the case just described. Myosin, however, has a much smaller molecular weight.

**Summary.** 1. An unusual case is reported in which purpura and sensitivity to cold were associated with a cold precipitable serum protein.

2. Similar cases previously reported are reviewed and discussed.

3. It is suggested that abnormal globulins may produce purpura, thrombosis,

oozing of blood from mucous membranes and sensitivity to cold as a result of their concentration in the blood and more particularly, their unusual solubility properties.

4. The term cryoglobulin is proposed to represent a group of proteins having the common property of precipitating (or gelifying) from cooled serum. If these proteins are in the serum in high concentration, they may precipitate spontaneously at room temperature.

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## STUDIES OF CRYOGLOBULINS

## II. THE SPONTANEOUS PRECIPITATION OF PROTEIN FROM SERUM AT 5° C IN VARIOUS DISEASE STATES

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THE literature contains but few reports dealing with the spontaneous precipitation of protein from serum. Serum turbidity due to precipitated protein may have been mistakenly considered lipid in nature in some instances.

Serum from normal fasting subjects is usually clear. When obtained 1 to 3 hours after a meal, it is generally turbid due to an increase in serum lipids. It has been reported<sup>12</sup> that the precipitate noted at times in cases of nephrosis consists largely of cholesterol with a small amount of protein.

When sterile serum is allowed to stand for several months, it usually becomes turbid due to a separation of lipids and protein from the colloidal state.

The present investigation has been concerned with the nature and significance, as well as the rate and degree, of spontaneous precipitation of protein from serum at 5° C. As noted in Paper I, the term cryoglobulin is proposed for the group of proteins having the common characteristic of precipitating in the cold. If the cryoglobulins occur in high concentration they may precipitate from serum at room temperature as in the case of purpura described in Paper I.

**Material and Methods.** Serums from 121 patients with a variety of pathologic conditions were studied. The serums from 35 conscientious objectors and 5 medical students served as controls. All blood samples

were obtained in the fasting state in the morning. The serums were placed in a refrigerator at 5° C. and observed once daily for 6 days to determine the presence or absence of cryoglobulin. One should be careful not to mistake a delayed fibrin clot for cryoglobulin precipitate. A fibrin clot will form as a discrete mass with the appearance of a gel which will not dissolve on warming to 37° C. The cryoglobulin precipitates, however, are composed of small discrete white particles which dissolve when the serum is warmed to 37° C.

If a precipitate formed in the serum, it was separated by centrifugation at 9° C. Further purification was attained by mixing the precipitate with 0.9% saline at 37° C. The precipitate would usually dissolve and reappear when the solution was cooled. This process was repeated twice, and the precipitate was finally dissolved in 0.01 N HCl for the purpose of further studies as noted in the following.

The cephalin-cholesterol test of Hanger<sup>3</sup> and the serum dilution test<sup>8</sup> were carried out on most of the serums studied. According to Hanger and co-workers<sup>4</sup> the gamma globulin fraction is responsible for the flocculation of the cephalin-cholesterol emulsion, the negative reaction in normal individuals being due to inhibition by normal constituents of the albumin fraction. It seemed desirable to ascertain whether there was any correlation between a positive cephalin-cholesterol test and the appearance of a cryoglobulin. The cephalin-cholesterol tests were not carried out on the control serums, which were assumed to be negative.

The serum dilution test is used to deter-

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mine an increase in euglobulins.<sup>8</sup> In this test the serum is diluted 100 times with distilled water. If there is an increase in serum euglobulins, a precipitate will appear in the diluted serum. According to Plotner<sup>8</sup> all serums giving a positive dilution test also give a positive Takata-Ara reaction. The dilution tests were made on most serums (including all control serums) to determine whether or not there was any relation between an increase in euglobulin and the presence of a cryoglobulin.

possible, however, to carry out some studies on 9 protein preparations from Grade 2 serums redissolved in dilute hydrochloric acid (Samples 2 to 10 in Table 2). The findings are given below.

*Solubility.* All of the protein preparations except No. 9 dissolved when mixed in 0.9% saline at 37° C. On cooling, the cryoglobulin reprecipitated. None of the warm saline solutions, however, was completely clear.

TABLE 1.—OCCURRENCE OF CRYOGLOBULIN PRECIPITATE IN PATHOLOGIC SERUMS COOLED TO 5° C

Grade	Cryoglobulin concentration (mg. %)	Time for appearance of precipitate
1 . . . . .	Trace to 6	24 hours—1 week
2 . . . . .	6 to 25	24 hours
3 . . . . .	Over 25	Immediately after cooling*

\* If present in high concentration (Grade 3), cryoglobulin may precipitate before the serum is cooled to below room temperature.

**RESULTS.** The pathologic serums were classified in 3 grades with respect to cryoglobulin precipitates as shown in Table 1.

Spontaneous precipitation of protein occurred in 31 of the 121 cooled serums obtained from the same number of cases of various diseases. Only 1 of the 31 positives was of Grade 3; this was the case described in Paper I. Twelve positive serums were of Grade 2. The remaining 18 positive serums were of Grade 1. The results of further studies of these serums are shown in Table 2. Precipitates were not found in any of the 40 control serums, and the serum dilution tests were negative.

It is of interest that although the cryoglobulins of Grades 1 and 2 were present in small concentrations, they were easily observed in the form of definite white precipitates.

It is evident from Table 2 that there is no correlation between the presence of cryoglobulins in serum and the reaction of the serum to the cephalin-cholesterol and serum dilution tests.

**PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE PROTEIN PRECIPITATES.** Since only small amounts of cryoglobulins were found in these serums, it was impossible to make detailed studies of the physical and chemical nature of these proteins. It was

When 0.01 N HCl was used as the solvent, the cryoglobulin dissolved readily and did not reprecipitate when the solutions were cooled at 5° C. However, only the cryoglobulin preparation from Case 9 gave a truly clear solution. The remaining solutions were slightly cloudy. On standing for 2 weeks at 5° C., 6 of the 8 cloudy solutions were clear enough for ultra-violet absorption studies. The substances responsible for the turbidity gradually settled to the bottom of the tube.

*Cholesterol Content.* Cholesterol determinations were made on the 2 most turbid of the 0.01 N HCl solutions (Nos. 2 and 10) by the method of Schoenheimer and Sperry.<sup>11</sup> Neither of the preparations contained any detectable amount of cholesterol.

*Phosphorus Content.* Three globulin solutions, Nos. 4, 7 and 8, were mixed together and a phosphorus determination was carried out on the resulting mixture by the procedure of Fiske and Subbarow.<sup>2</sup> No phosphorus was detected.

*Quantitative Protein Determinations.* Colorimetric determinations of the proteins in the 0.01 N HCl solutions were made with the phenol reagent,<sup>9</sup> the cryoglobulin of the patient J. P., as reported in Paper I, being used as the standard.



The values for cryoglobulin, as thus obtained, are listed in Table 2.

*Ultraviolet Absorption.* Seven of the 0.01 N HCl solutions of cryoglobulins were sufficiently clear for ultraviolet absorption studies. The densities over the range 2400 to 3300 Å were determined with a Beckman quartz spectrophotom-

limits; so only the average curve was used to represent these proteins.

By comparing the ultraviolet absorption spectra of the cryoglobulin preparations with those of the normal plasma proteins<sup>6</sup> it is evident that the cryoglobulins differ from albumin. Five of the cryoglobulin preparations gave absorption curves sim-

TABLE 2.—CASES WITH POSITIVE CRYOGLOBULIN, CEPHALIN-CHOLESTEROL, OR SERUM DILUTION TESTS

Case No.	Diagnosis	Grade of cryoglobulin precipitate	Cryoglobulin (mg. %) (serum)	Cephalin-cholesterol test (48 hrs.)	Serum dilution test (48 hrs.)
1	Cryoglobulinemia and cardiovascular renal disease	3	800	0	
2	Lymphatic leukemia	2	25	0	0
3	Congenital hypoprothrombinemia	2	6.9	2	0
4	Bronchopneumonia	2	7.6	0	0
5	Bronchiectasis	2	20	0	0
6	Rheumatic heart disease	2	12	0	0
7	" " "	2	12	0	0
8	Subacute bacterial endocarditis	2	21	0	0
9	" " "	2	19		
10	" " "	2	25	4	2
11	" " "	2	..	2	0
12	" " "	2	..	2	0
13	" " "	2	..	0	1
14	Rheumatic heart disease	1	Trace	0	0
15	" " "	1	Trace	0	0
15	Pneumonia	1	Trace	0	0
17	Pleural effusion	1	Trace	0	0
18	Empyema (tbc)	1	Trace	0	
19	Emphysema	1	Trace		
20	Cardiovascular renal disease	1	Trace	0	0
21	Brucellosis	1	Trace	0	0
22	Ulcerative colitis	1	Trace	0	
23	Embolio femoral artery occlusion	1	Trace	0	
24	Hepatic cirrhosis	1	Trace	4	0
25	Diabetes	1	Trace	0	
26	"	1	Trace	0	0
27	Addison's disease	1	Trace	0	0
28	Polycythemia vera	1	Trace	0	0
29	Idiopathic purpura	1	Trace	3	1
30	Carcinoma of pancreas	1	Trace	0	0
31	Lymphatic leukemia	1	Trace	0	2
32	Myeloid leukemia	0	0	3	0
33	Hodgkin's disease	0	0	3	0
34	Polycythemia vera	0	0	3	0
35	Carcinoma of pancreas	0	0	2	0
36	Multiple myeloma	0	0	0	2
37	" "	0	0	..	2

eter with a hydrogen discharge tube and quartz cuvettes 1 cm. in thickness. Using the results of the quantitative determinations of these proteins, it was possible to calculate the ultraviolet extinction coefficients (Fig. 1). The extinction coefficients of the cryoglobulin from Samples 7, 8 and 9 were identical within experimental

limits; so only the average curve was used to represent these proteins.

The absorption curve for the cryoglobulin from the case of familial hypoprothrombinemia (No. 3) is similar to that of a nucleoprotein.\* A quantitative Bial's test for ribose was carried out on this

\* C. P. Barnum (unpublished data).

preparation. Five per cent of the protein appeared to be ribose. This may indicate that the protein was a nucleoprotein, but only a very small amount of material was available, and the Bial's test may not have been specific for ribose. The electrophoretic pattern of the plasma proteins of this case was essentially normal.

approximating that of fibrinogen, it is likely that these proteins are not fibrinogen.<sup>7</sup> Since most of the spontaneously precipitated proteins have ultraviolet absorption curves similar to those of the gamma globulins, these proteins probably belong to the gamma globulin group. The cryo-

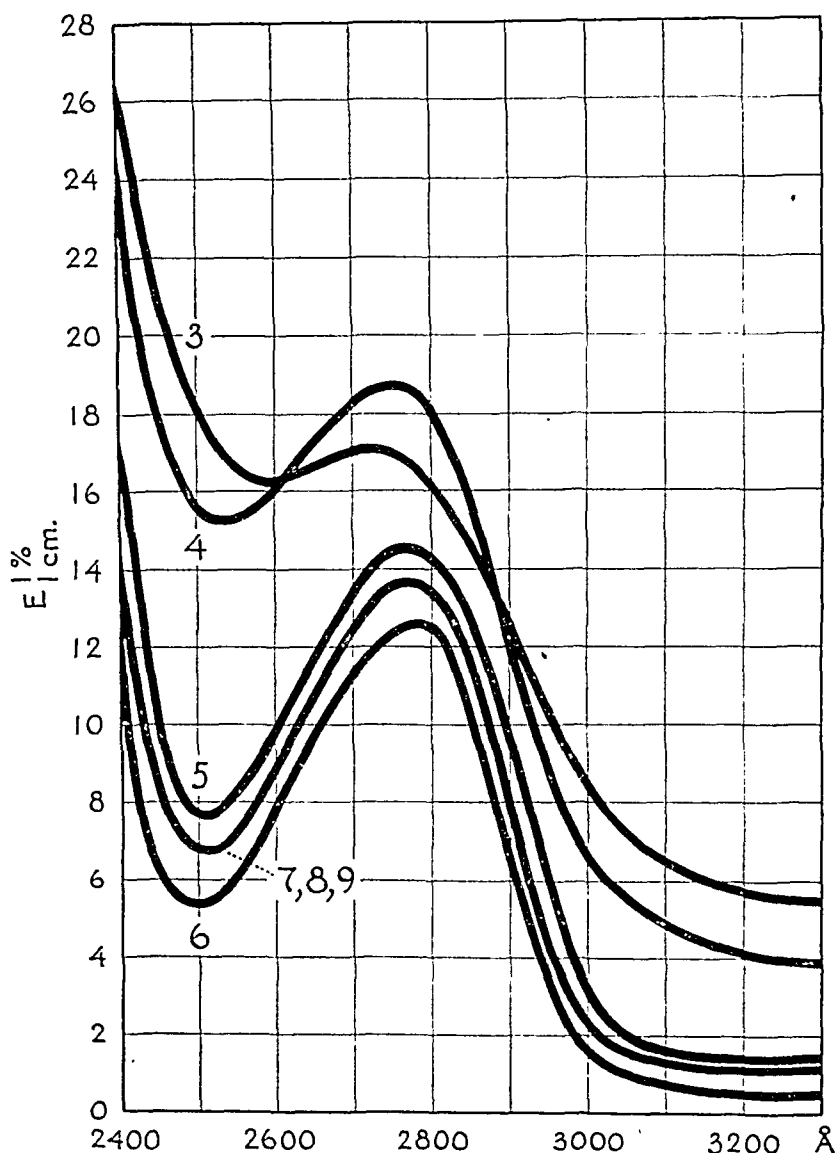


Fig. 1.—Ultraviolet extinction coefficients for cryoglobulins of Samples 3 to 9 inclusive. These were determined with a Beckman quartz spectrophotometer with a hydrogen discharge tube.

**Discussion.** The present results indicate that several different proteins may precipitate spontaneously from cooled abnormal serum. In view of the fact that none of the proteins from the cases discussed in Paper I had a molecular weight even

globulin isolated from the case of hypoprothrombinemia may be a nucleoprotein.

It is evident that cryoglobulins may be present in the serum of patients with a great variety of diseases, while normal serum does not appear to contain this

type of protein. The concentration of cryoglobulin in pathologic serum is quite variable. In some cases it is present in such large quantities that it may well relate to the patient's symptoms and findings as in the case reported in the preceding paper. Cryoglobulinemia may be considered a non-specific indication of a disease process comparable to fever, increased erythrocyte sedimentation velocity, and other symptoms.

Stein and Wertheimer<sup>12</sup> reported that 5 of 7 cases of subacute bacterial endocarditis exhibited protein precipitates in cooled serum. They suggested that this may be of diagnostic significance. However, since cryoglobulins occur in the serum of patients having a great variety of diseases, their presence is of doubtful significance in any specific sense. In the present study the serums from 6 cases of subacute bacterial endocarditis were studied. In all of these (Table 2) cryoglobulin was observed in the cooled serum. The diagnosis in 1 case (No. 13) was not definitely established, *i. e.*, positive blood cultures could not be obtained. In another case (No. 8) a marked reduction of cryoglobulin in the serum was apparent after 3 weeks of penicillin therapy. Visually, the smallest concentration of cryoglobulin was present in Case 11. This patient had been treated with penicillin for several weeks before the serum was studied for cryoglobulin. These results indicate that cryoglobulinemia is at least a very common finding in this disease, although probably not uniformly present.

There are 2 reports in the literature of patients with purpura hemorrhagica associated with cold allergy.<sup>5,10</sup> The histories and clinical findings in these 2 cases are quite similar to those of J. P. (see Paper 1). There are also reports of cases with sensitivity to cold with urticarial lesions and "red blotches."<sup>13</sup> It is unfortunate that no observations were made on the cooled serum from these patients. At present one can only speculate on the presence of cryoglobulinemia in these instances.

Coburn and Moore<sup>1</sup> have recently shown

that there is an increase in serum gamma globulin in patients with lupus erythematosus. They also observed that in the descending limb of the electrophoresis cell, where the other proteins moved away from the gamma globulins, there was an opaque precipitate. This suggests the presence of a cryoglobulin in the serum of their cases.

Abnormally large amounts of gamma globulin occur in hyperimmune antipneumococcus horse serums and in the serums of cases of liver disease, multiple myeloma, sarcoidosis, lymphopathia venereum, and lupus erythematosus. Since most of the cryoglobulins probably belong to the gamma globulin group, it would be of interest to study the serums from patients with these diseases. One should bear in mind, however, that an increase in gamma globulin does not necessarily indicate the presence of cryoglobulin. This is shown by the lack of correlation between the cephalin-cholesterol flocculation test and the occurrence of cryoglobulin. In 1 case of hepatic cirrhosis, not included in the foregoing, the cephalin-cholesterol flocculation was markedly positive as was also the thymol turbidity test. The serum globulin in this case ranged between 8 to 10 gm. %, most of which was revealed electrophoretically to be gamma globulin; yet no cryoglobulin was present.

*Lipid Turbidity.* On several occasions fresh fasting serums were observed to be turbid. After these turbid serums were kept at 5° C. for 1 to 3 weeks, a precipitate formed on the surface as a white ring. This was observed in 7 serums from a variety of cases: glomerulonephritis, leukemia, pneumonia, diabetes and aplastic anemia. The substance appearing on the surface was assumed to be of lipid character. Its behavior was entirely different from the cryoglobulins.

Eleven diabetic serums were studied. These were collected in the fasting state. Only 1 of the freshly prepared serums was turbid, but after the serums were kept at 5° C. for 48 hours, 8 became turbid. Again, as these stood at 5° C. for longer

periods, a precipitate formed on the surface as a white ring, the serum below remaining clear.

Most serums are turbid when obtained shortly after a meal. Upon standing for 1 to 2 days the lipids in these serums rise to the surface.

**Summary.** 1. In a study of 121 serums from as many individuals, suffering from a variety of pathologic conditions, spontaneous precipitation of protein from the cooled serum was observed in 31 instances. The presence of these proteins, which are designated as cryoglobulins, may be regarded as a non-specific indication of a disease process. They were not encountered

in any of the serums from 40 normal individuals.

2. Serums which contained cryoglobulins were divided arbitrarily into 3 grades on the basis of amounts. These are as follows:

Grade 1	From a trace to 6 mg. %
Grade 2	From 6 to 25 mg. %
Grade 3	Greater than 25 mg. %

Grade 3 cryoglobulinemia was encountered in but 1 case, and in this instance there is reason to believe that the cryoglobulin was related to a severe purpura which stood in the foreground of the clinical picture.

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## HEPATIC CALCULI

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HEPATIC calculi (hepato-lithiasis) have been rarely diagnosed clinically, are usually unsuspected, and found only at operation or necropsy. The literature, especially American, on this subject is sparse, yet Best<sup>2</sup> in an analysis of the literature states that in 456 cases of cholelithiasis there were 35 cases of liver stone. This represents an incidence of liver stones in cholelithiasis of 7.6%. Courvoisier (1903) in 16,025 autopsies found 1714 cases of cholelithiasis in which there occurred 1 case of liver stone. Hesse<sup>7</sup> (1911) in 17,402 autopsies had 278 cases of cholelithiasis and 1 case of liver stones. However, Miyake<sup>8</sup> (1913) in 257 cases of cholelithiasis had 20 cases of liver stones. Apparently in Japan, liver stones are relatively frequent. Hepatic calculi may also occur without cholelithiasis. In 53 cases of liver stones analyzed by Ruffanov,<sup>9</sup> 20% had calculi confined to the liver alone, while 80% had calculi also present in the gall bladder, bile passages or both. The present paper briefly reviews the subject of hepatic calculi and describes 4 cases. It also discusses the possibility of diagnosis, and the clinical significance of this condition.

CLASSIFICATION OF HEPATIC CALCULI. Liver stones may be grouped as follows:

1. Firmly fixed stones within the intra-hepatic ducts. These may be single or multiple and the size of the calculi varies widely.
2. Isolated, circumscribed lesions in the liver with stones embedded in a cavity containing bile or pus.
3. A more diffuse process with the intra-hepatic ducts containing small stones, gravel or debris.
4. Diffused, small abscesses containing stones or gravel and associated with a purulent cholangitis.

INCIDENCE. It has already been stated that liver stones have been found in as many as 7.6% of cases of cholelithiasis which came to necropsy. This incidence would seem to vary directly with the thoroughness with which all the bile ducts of the liver are examined. Hepatic calculi have been described in every decade from the 2nd to the 9th. In contrast to gall stones, there is no difference in rate of occurrence of hepatic calculi between the sexes.

ETIOLOGY AND PATHOGENESIS. The etiology of hepatic calculi is not definitely known. The various theories advanced for the genesis of gall stones apply equally to liver stones. These may be summarized as infection, stasis, disturbed metabolism (especially that of cholesterol), abnormalities in the chemistry of bile, dysfunction of the autonomic nervous system, and, perhaps, changes in the hepatic cell membrane. The immediate mechanism causing the formation of stones is probably chemical,<sup>3</sup> due to variations in the ratio of concentration of bile acids, fatty acids, cholesterol, calcium and protein, together with changes in the pH of bile. Hepatic calculi are usually of the bilirubin-calcium type<sup>13</sup> but they may have variations similar to those found elsewhere in the biliary system.

CLINICAL ASPECTS. The symptoms vary widely from the symptomless to those showing evidence of biliary obstruction. Since the majority of patients have co-existing stones in the gall bladder and/or bile ducts, it is difficult to describe characteristic symptoms of hepatolithiasis. The most frequent symptom is pain, usually epigastric or in the right upper quadrant, occasionally radiating to the right scapula. This pain occurs in attacks which may be of long duration. Fever is the next most

common finding, and in 25 % of cases there are chills. These, when they occur, are due to cholangitis, liver abscesses or pleurisy. The temperatures may be normal in uncomplicated hepatolithiasis. Jaundice is frequently encountered, is of the obstructive type, and may be accompanied by pruritus, hemorrhage and changes in the urine and stool. Gastric disturbances are frequent, indigestion, anorexia and vomiting during attacks are the rule. Very often inanition and anorexia are the earliest symptoms of hepatic calculi. With stones also present in the biliary tract, the symptoms would be more inclined to be those of cholecystitis or obstruction of the biliary passages, the stones in the liver causing no symptoms except those of a general nature (inanition, anemia, fatigue, etc.). The liver, or one of its lobes, is usually enlarged, but it may be normal in size. There may or may not be tenderness and spasm on palpation of the abdominal wall. Achylia is common. In secondary involvement of other organs we find chronic, secondary, indurative pancreatitis, which seems to be less than that found in cholecystitis. A right-sided pleural involvement with serous or purulent exudate may occur, and damaged kidneys have been reported.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS.** It is readily noted that there is no pathognomonic symptom complex for this condition. Clinically, the diagnosis of hepatic calculi is at best difficult, if not impossible without the Roentgen ray. There may be a complete absence of symptoms. With symptoms, the differential diagnosis includes cholecystitis, cholelithiasis, obstruction of the common duct, cholangitis, liver abscess and other diseases of the gall bladder and bile ducts.

The roentgenogram affords a much more accurate means of diagnosis. Walters and Snell<sup>13</sup> suggest that small irregular opacities occasionally seen in the hepatic area on Roentgen ray may be due to intraductal stones. Volpe<sup>12</sup> described a solitary hepatic calculus as a mulberry-like shadow. The hepatic calculi in our Case 1 are almost

uniformly spherical in appearance, varying in diameter from 0.5 to 2 cm. There is an outer shell of rather dense calcification. The core is much less opaque and is studded with round areas of radiolucency. These are probably due to an irregularity in the deposition of calcium, but there is a possibility that the calculi are canalized by bile.

Other causes of calcification in the liver must be considered in the differential diagnosis. These include: (1) Hemangiomas: hemangiomas of the liver are almost always of the cavernous type. When they calcify they exhibit numerous trabeculations arising and radiating from a common center.<sup>1</sup>

2. Amebic abscess: calcification occasionally occurs in chronic abscesses. There is almost always a history of amebic infection and the calcification is in the form of dense irregular shadows.<sup>10</sup>

3. Echinococcus cyst: in chronic cysts, calcification may occur in the capsule. The calcification is in the form of concentric strips alternating with transparent strips.<sup>4</sup>

4. Gummata: gummata usually do not calcify. When calcification does occur, it is usually trabecular in nature.<sup>5</sup> There is evidence of lues elsewhere.

5. Tuberculomas: there is almost always evidence of tuberculosis elsewhere, including calcified tuberculomas of the spleen. They appear as spheres with a central density having a surrounding moat.<sup>5,11</sup>

6. Carcinoma: Hamburger<sup>6</sup> described a calcified primary carcinoma of the liver in a 5 year old child. The calcification was attributed to irradiation of the tumor.

7. Hydatid cysts, calcified subphrenic abscesses, calcified infective granulomata, calcified infarcts and metastases should be readily differentiated from hepatic calculi by the character of their appearance, their location and the clinical picture.

**Treatment and Prognosis.** The treatment of hepatic calculi will vary greatly with the individual patient. In those cases with no symptoms, or with minimal

symptoms and no stones in the extra-hepatic biliary system conservative treatment is indicated. This would include a low fat, high carbohydrate, high protein diet with adequate vitamin intake. Operative treatment depends in great degree on associated findings such as gall stones, common duct stones, etc. Rufanov<sup>9</sup> in analyzing 55 cases states that the most frequently performed operations were cholecystectomy, choledochotomy, hepaticotomy and cholecystostomy. According to Rufanov<sup>9</sup> the overall mortality of cases undergoing surgery is 60 to 65%. The best prognosis is in the younger age group (under 50 years) who have had a relatively short duration of illness (under 3 years). In these cases the pathologic process is usually limited in extent and there is no general damage or insufficiency of the liver parenchyma.

The highest operative mortality occurs in people over 50 years of age. Usually the disease is of long duration and there are severe pathologic changes in the liver and other organs (kidney, pancreas, etc.). Ninety per cent of these cases have coexisting stones in the gall bladder and at autopsy all the bile ducts to their most minute branches are filled with compactly packed stones.

Another group may be mentioned, namely elderly people who have had prolonged symptoms of cholelithiasis with or without duct obstruction and have not undergone surgery. These are usually seen shortly before autopsy and a severe cholangitis, liver or subdiaphragmatic abscess, ulceration of the gall bladder or bile ducts, cholemia, hemorrhage, sepsis and collapse are encountered.

The principal causes of postoperative death are hepatic insufficiency or a purulent process, *c. g.*, cholangitis, liver abscess. Second laparotomies are greater in number in hepatolithiasis than in cholelithiasis. This is due to the severity of the liver stone pathology, to overlooking the presence of liver stones at the time of original operation, and to short periods of drainage of the ducts.

**Case Report.** CASE 1. (Referred by Dr. Atwood, Boston, Mass.) A married woman of 62, mother of 2 children, has been under Dr. B's care for 29 years. When first seen in 1917 when she was 33 years of age she gave the history of appendectomy for an acute appendicitis 7 years before and removal of a cervical rib when 2 years of age. She stated that "she had not felt well since her last child was born, and was suffering from constipation, poor endurance, fainting spells and occasional vomiting." She was allergic to fish, complained of intestinal gas, passing mucus from rectum, and dizzy spells with attacks of cardiac palpitation. She weighed 89 pounds; a reduction of the best weight she ever had of 11 pounds; her blood pressure was 117/88. The diagnosis made at that time was vicerptosis, ileocolonic stasis, neurosis and general debility. As a result of bed rest, abdominal support, and medications she improved and reached a weight of 117 pounds in a few months time.

She was referred back to Dr. Atwood, and living some distance from New York, was seen at about yearly intervals without anything of moment occurring. In 1931 the menopause began, with the usual vasomotor symptoms which were controlled by ovarian extracts. About that time she developed anemia, the red cells dropping as low as 2,700,000 per c.mm. This was controlled by hematinics and diet.

Up to 1939 the diagnoses made and treatments employed were for indigestion, slight anemia, debility, periods of exhaustion, vague abdominal pains, arthritic pains due to a slight degree of arthritis of the atrophic type, constipation and insomnia.

In 1939, after about 2 years of complaints of more fatigue and indigestion, she was re-examined thoroughly. There were 2 abscessed teeth, there was a moderate fusiform dilatation of the aorta. The blood pressure was 150/86. The liver was not enlarged or tender. The Wassermann was negative. Laboratory findings included: blood sugar, 109 mg.; non-protein nitrogen, 33 mg.; calcium, 11.3 mg. (top normal); phosphorus, 3.5 mg.; cholesterol, 280 mg. (normal 125 to 210); uric acid, 3.2 mg.; and total protein, 8.4 gm. per 100 cc. A slight hypochromic anemia was present. The stomach was achylic even to histamine and Dr. B's pancreatic test was half normal in amylase units. The liver function tests were normal

(bromsulphalein, cephalin flocculation, hippuric acid) as were also the urine and feces. The Roentgen rays were not particularly significant with the exception of the liver, which showed a number of calculi scattered throughout the organ. Several Roentgen ray examinations of the liver were made since 1939 showing continuously about the same condition throughout the years.

She never had any definite symptoms pertaining to the liver and is today about in the same reasonable state of health as she has been for years.

CASE 2. A 77 year old white female was first admitted to St. Vincent's Hospital, New York City, in August 1938, because of dyspnea and epigastric pain of 1 day's dura-



FIG. 1.—Film taken in 1939 showing liver stones. Gall bladder normal.

*Comment.* Here was a physically unendowed woman with a series of minor complaints over years of time. The time of onset of the liver stones is not known. It is possible that the anemia or exhaustion was in some way bound up with their advent. The fact that stones may occur in the liver and there be none in the gall bladder or ducts suggests that an abnormal metabolic process may occur in the liver cells. The high content of blood calcium and cholesterol seems significant.

tion. Except for an operation 40 years previously because of an ovarian cyst, she had always enjoyed good health. There was no history of jaundice or biliary colic. Physical examination revealed an elderly, thin female in moderate respiratory distress. The positive physical findings were limited to the heart and lungs. The heart was enlarged, especially the left ventricle, as was the aorta. The rhythm was irregular and the blood pressure was 170/90. There were fine moist râles at both lung bases. The abdomen was negative and the liver not



enlarged. The urine showed 3+ albumin, 30 leukocytes per high power field and a specific gravity of 1.015. The blood count showed 4,400,000 red cells, 14 Gm. hemoglobin, 10,200 leukocytes, with 88% neutrophils, 11% lymphocytes and 1% eosinophils. Blood non-protein nitrogen and sugar were 48 mg. and 82 mg., respectively, per 100 cc. and the Kahn reaction was negative.

bases. Her heart was unchanged from the first admission. The liver was enlarged 5 finger breadths below the costal margin, was smooth and slightly tender. The blood count showed 3,300,000 red cells, 70% hemoglobin, 19,200 leukocytes with 76% neutrophils. The non-protein nitrogen was 32 mg. and the icteric index 32. For the 1st week, the temperature ranged between 100° and



FIG. 2.—Postero-anterior film taken in 1946 showing the same as above. Gall bladder films taken separately still show a normal gall bladder.

She was digitalized and rapidly improved and was discharged from the hospital in 1 month.

The second admission was in May 1939, following severe pain in the left posterior chest with slight fever of 5 days duration. She had been dyspneic for the preceding 4 months. At the time of admission she was acutely ill, dyspneic, orthopneic and the skin was jaundiced. The positive physical findings were moderate dependent edema, dullness and diminished breath sounds in the left lower lobe and râles at both lung

102° F. She gradually became compensated on digitalis and diuretics and the jaundice disappeared. She was discharged 1½ months after admission.

The last admission was in February 1940, when she suffered a cerebral vascular accident. She was comatose on admission and died shortly thereafter at the age of 79.

At autopsy, cerebral atherosclerosis and (ncephalomalacia and hemorrhage in the left parietal and frontal lobes were found to be the immediate cause of death. The heart was hypertrophied and dilated. There was



FIG. 3.—Right lateral film taken in 1946.

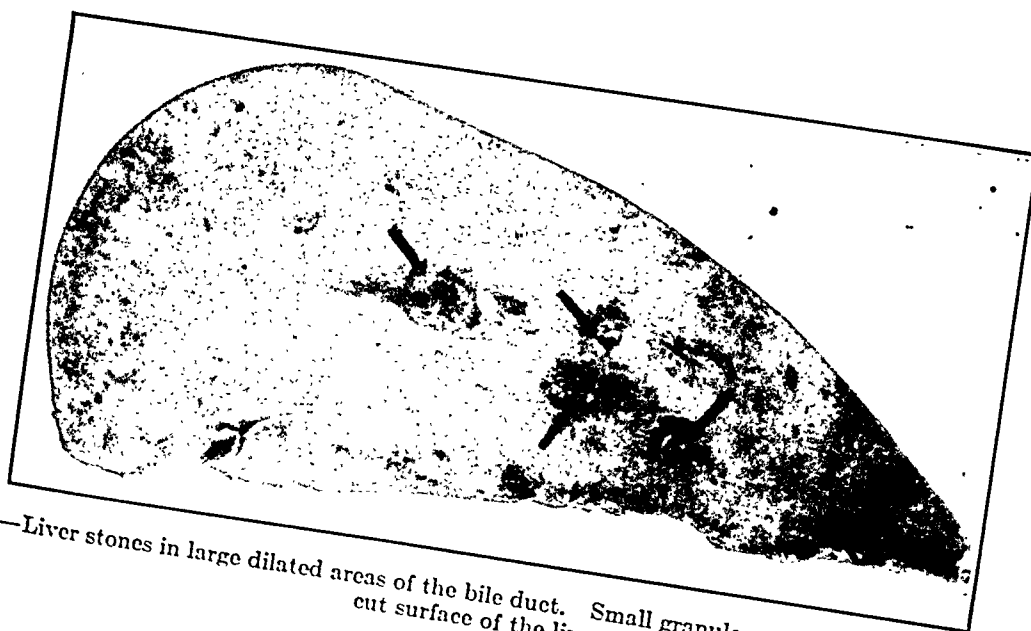


FIG. 4.—Liver stones in large dilated areas of the bile duct. Small granules of stone scattered over the cut surface of the liver.

acute verrucous endocarditis of the aortic cusps. There was a lobular pneumonia of the lungs. The liver (Fig. 4) was not enlarged, weighing 1100 gm. The surface was smooth and on section was yellow-brown in color. The bile ducts in the right and left lobes close to the hilus were dilated and filled with faceted, pigmented stones. Microscopically the liver lobules were atrophied, especially in the central portions.

The gall bladder was filled with pigmented faceted stones. The common duct and both hepatic ducts were dilated and contained the same faceted stones. There was apparently no obstruction to the flow of bile.

*Comment.* In this familiar type of cardiac case it is probable that at the second admission the icterus may have come from a pulmonary embolism and not from the calcareous condition in the liver and biliary tract. In the second admission her liver was definitely enlarged, probably due to heart failure. The death was due to an apoplexy. From the first to the third admission there were no definite clinical signs of either liver or gall bladder stones and the liver was not enlarged at the last admission, as it had been at the second, 9 months before. Considering the history before her first admission, she was in "good health" even though she must have had both liver and biliary tract stones for years.

CASE 3. A dentist, 42 years of age, with a past history of pains in his upper right abdomen and right scapular region for about 6 years before, was seen by Dr. B. His general health was only fair and he had periods of exhaustion which caused him to stop work for a few weeks until he became "bucked up." He continued at his work until 4 months before first seen by Dr. B., when he stated that as a "result of a fire in his office he became jaundiced." This cleared in about 3 weeks time. However, he had an attack of jaundice 1 year before following an operation for rectal fistula, and when seen first he had had his third attack of jaundice, existing for about 4 weeks.

Briefly, he was a jaundiced individual in a fair state of nutrition but showed a rapid sedimentation rate, a diphasic temperature and attacks of chills. A leukocytosis (19,000)

and high neutrophil count (84%) suggested an infection. The Roentgen rays showed about 11 small stones scattered through his liver, mostly in the lower portion of the organ. These seemed to be solid stones high in calcium. He became ill quickly and was hospitalized, treated medically with the diagnosis of a possible septic cholangitis. He made a symptomatic recovery in 4 weeks and went back to work in his office. About 3 weeks later he began complaining again, became moderately jaundiced and septic, and was operated upon by Dr. John F. Erdman who removed his gall bladder, appendix and established tube drainage. The tissue diagnoses were chronic cholecystitis without gall stones, acute periportal hepatitis, miliary abscesses of the liver and chronic appendicitis. The man recovered slowly, the wound healed perfectly and he went to a rest home. About 7 months after the operation there developed small growths along the upper half of the scar which were found to be "metastatic adenocarcinoma of the skin." At the time of the operation there was no evidence in his abdomen of malignant disease.

*Comment.* It seems reasonable to assume in this case that the liver stones had existed for years and, other than the possibility that the periods of exhaustion were due to them, gave no symptoms. The Roentgen ray evidence of hepatic calculi and findings at operation suggest that the abscesses of the liver may have resulted from these stones, although it is more probable that they occurred from the septic cholangitis. The site of the carcinoma from which he succumbed was not determined.

CASE 4. In 1931 a migrainous woman, 52 years of age, with 3 children, was treated by Dr. B. for a biotoxic intestinal condition. Her past history revealed that at the age of 25, after the birth of a child, she began complaining of gaseous indigestion and pain in the upper right abdomen. At 38 years of age cholecystectomy and appendectomy were performed, the gall bladder containing many stones. She had a reasonable degree of relief for 4 years, when gradually attacks of gas, anorexia, constipation and loss of weight returned. These were her complaints

when first seen. At subsequent examinations, after Roentgen ray, a diagnosis was made of liver stones. They were small in size and scattered throughout the liver like birdshot.

About 1 year later she became jaundiced. Examination of the biliary tract after the ingestion of dye revealed the extrahepatic ducts to be dilated and stones were outlined. Under conservative treatment the jaundice cleared but she never regained her former state of health.

At 63 years of age (1942) her health failed perceptibly. At times the liver was enlarged and tender. She ran a low grade fever from time to time and had recurrent mild attacks of jaundice. The icteric index was always above normal. The highest hippuric acid in 4 hours was found to be 4.7 gm. and the galactose tolerance in 5 hours was 0.3 mg.

For a period of months there was a marked abatement of symptoms, the liver function tests were normal, but the icteric index remained high. Her complaints gradually returned and, finally, after 2 weeks of pre-operative preparation, she was operated upon by Dr. Raymond P. Sullivan in 1943 at the age of 64. At operation innumerable small stones of varying sizes were removed from the extrahepatic biliary ducts. They choked the ducts practically to the under surface of the liver. After removal of the T tube several more stones came out. The stones were calcium-bilirubin in character. No stones could be palpated in the liver substance at operation. She has greatly improved symptomatically in the past 3½ years. Roentgen ray still reveals the presence of stones in the liver.

*Comment.* It may be concluded from her physical and symptomatic improvement following operation, that her symptoms were due to the stones in the biliary tract and not to those in the liver. The icteric index is now at the upper limit of normal. The stones still remaining in the liver seem to produce no symptoms, although a mild degree of anemia and slight fatigue still persist.

*Discussion.* In Case 1 (uncomplicated hepatic calculi) the liver was not enlarged or tender and there were no symptoms suggesting the presence of hepatic stones. The only symptoms were general, suggest-

ing a vague type of indigestion which could not be distinguished from those present in achylia or a low-grade pancreatitis. This case is also of interest because of the absence of stones in the extrahepatic ducts and gall bladder. Case 3 also had no extrahepatic stones, although the gall bladder was infected. The other 2 cases had both intra- and extrahepatic stones.

Hepatic insufficiency did not occur in Case 1 or 2 and both cases gave no specific symptoms relative to the biliary system. (It is assumed that the transient jaundice in Case 2 was due to a pulmonary infarct.) Both Case 3 and 4 had symptoms, 1 due to infection and the other to gall duct obstruction and mild infection. Thus we may say that in uncomplicated hepatic calculi the symptoms are minimal or absent. When symptoms occur, they are due to infection. In hepatic calculi complicated with extrahepatic biliary calculi, symptoms referable to the biliary system are more likely to occur and are indistinguishable from those produced by disease of the gall bladder or common duct in which no liver stones are present.

The only positive method of diagnosis is by roentgenogram, and unless the liver stones are calcified or of considerable size, they will not be discovered. In view of the statistics quoted earlier in this paper, it appears that a painstaking search of the intrahepatic ducts at autopsy, especially in cases of cholelithiasis, will reveal a much greater incidence of hepatic calculi than is at present thought to exist.

True uncomplicated hepatic calculi appear to be compatible with long life and comparative good health and the treatment should be conservative and supportive. It is reasonable to assume, if there is but a single hepatic stone or a cluster of stones in a small area, that their removal by operation should be considered. In the presence of complications such as liver abscess, cholelithiasis, cholangitis and obstruction of the common duct, the treatment should be predicated on the complication and the presence of the liver stones be considered as of secondary im-

portance. However, it must be remembered that in the presence of liver stones the mortality rate in operations of the biliary tract is increased.

**Summary.** The incidence of hepatic calculi associated with cholelithiasis is probably about 6% when careful studies of the intrahepatic ducts are made at autopsy. The incidence is about equal for male and female. Hepatic calculi produce no characteristic symptoms. Usually symptoms are caused by associated stones in the extrahepatic biliary system or by complications such as infection. The diagnosis can only be made by roentgenogram.

Of 4 cases of hepatic calculi here presented, 2 were symptomless, although 1 of these also had stones in the extrahepatic

biliary system. One case was complicated by infection (multiple small liver abscesses) and 1 case by obstruction of the common duct which was relieved by operation, and the stones remaining in the liver have now been asymptomatic for several years.

In true hepatic calculi with no complications, treatment is conservative and the prognosis is good. With complications such as obstruction or infection, surgical treatment should be directed toward the complication, in which case the mortality is greater than if no hepatic calculi are present. The principal causes of postoperative death are hepatic insufficiency or a purulent process, and as cholangitis and liver abscess.

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## STUDIES OF HEPATIC FUNCTION IN PULMONARY TUBERCULOSIS

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CHRONIC pulmonary tuberculosis although a localized disease will cause changes in other organs of the body by metastatic bacterial or toxic action. Pathologic changes in the liver are found not infrequently on postmortem examination. Together with chronic alcoholism pulmonary tuberculosis is the most frequent cause of fatty infiltration of the liver. In contrast to these findings there is no direct clinical evidence of significant liver damage in patients with chronic pulmonary tuberculosis. This apparent discrepancy stimulated the interest in functional liver studies in pulmonary tuberculosis and during the last 25 years a number of investigations were published concomitant with the development and perfection of liver function tests.

A review of these studies reveals that again in contradiction to the clinical observation considerable laboratory evidence of liver function disturbance was found. Lichtman<sup>5</sup> in his classical book on diseases of the liver states therefore, "while clinical evidence points to a lack of significant hepatic parenchymal damage in patients with pulmonary tuberculosis, sensitive liver function tests indicate the opposite." A critical study of these publications shows however that the function tests used were mostly non-specific and partly obsolete. This applies to the first publications in this field which appeared in the French literature,<sup>1</sup> as well as to the series of studies by Steidl and Heise,<sup>8a,b</sup> in this country. These authors found pathologic readings in most cases of far-advanced tuberculosis and in a later study almost identical results in patients with moderate and minimal involvement. It is interest-

ing to note that whereas they found positive results with non-specific tests, *f.i.*, the Congo red test or since then discarded procedures such as the oxidation test, the bromsulphalein test as used in its original modification did not give any pathologic readings.

In a subsequent study by 2 other authors<sup>4</sup> the same test, 2 mg. dose, showed however some evidence of hepatic dysfunction. In 1942 by using the more sensitive 5 mg. per kg. test, Kruger and Gerber<sup>3</sup> found evidence of impaired function, especially in far-advanced protracted disease. They examined also a series of 20 patients with secondary amyloid disease and found significant retention of bromsulphalein in 18 patients. In contrast to their findings a previous study<sup>9</sup>, which was entirely limited to patients with pulmonary tuberculosis and complicating amyloid disease, showed dye retention only in 2 out of 12 patients. These authors used however the original 2 mg. dose procedure.

The 3 last-mentioned studies showing negative results with the 2 mg. dose of bromsulphalein even in the presence of marked pathologic anatomic changes as in complicating amyloidosis, and demonstrating definite disturbance with the more sensitive 5 mg. dose modification, seem to point the way to a clarification of the problem. We felt that with the further improvement of the test in the form of the serial bromsulphalein test and also the other fairly specific tests as the intravenous hippuric acid test, the cholesterol ester determination, the cephalin cholesterol flocculation and the determination of a series of chemical serum compo-

nents related to liver function, a satisfactory result could be obtained. Based on the symposium on liver function tests<sup>6</sup> and the recent work on liver impairment in acute disease,<sup>7</sup> we set up a study of liver function in a group of far-advanced cases, utilizing the following tests and laboratory procedures.

**Method.** At first it was decided to select patients falling into the minimal, moderate, and far-advanced stages of tuberculosis. Later this was changed to include only a group of patients with far-advanced disease and without complicating tuberculous empyema or amyloidosis. All patients included in this series were carefully interviewed for previous history of jaundice or biliary colic. In addition, an excretory cholecystogram was done to rule out stones, and delayed emptying time of the gall bladder dye. Priodax was used with the standard technique advised.

**Program.** 1st day. 7 A.M. Patient urinates and discards specimen. All urine for succeeding 24 hours is collected in a brown bottle supplied by laboratory. This bottle contains 5 gm. of  $\text{Na}_2\text{CO}_3$  and 100 cc. of petroleum ether. Bottle must be kept out of intense light. (Urobilinogen.) 7:15 A.M. 15 cc. of blood drawn for cephalin cholesterol, bilirubin, cholesterol (total and ester) and phosphatase.

2nd day. 7 A.M. Patient urinates to complete 24 hour specimen. 7:15 A.M. 13 cc. of blood drawn for NPN, albumin, globulin and fibrinogen. 7:30 A.M. Serial bromsulphalein test.

3rd day. 7:30 A.M. Intravenous hippuric acid test.

**Results.** In Table 1, attention is called to the fact that the non-protein nitrogen was within normal limits in every instance. Similarly, the total serum proteins were all in the upper levels of normal with normal albumin, globulin and fibrinogen amounts and ratios. While these figures cannot be used as a true index of nutritional status, they at least show that the nitrogen levels were maintained.

In regard to bilirubin, normal values for circulating bilirubin vary within wide limits. According to Lichtman,<sup>5</sup> values up to 0.5 mg. % have been found in nor-

mal healthy humans, while Cantarow and Trumper<sup>2</sup> quote up to 0.8 mg. as the high norm, with 75% of cases being below 0.5 mg. In this small series, figures ran from 0.13 to 0.60 mg., none high enough to be impressive. As for urobilinogen, normal values of 1 to 4 mg. are usually eliminated daily in the urine and our figures varied from 0.09 to 2.76 mg., again within normal limits.

In Table 2, figures are given for the same 12 patients for studies in cholesterol as total free esters, and free as calculated for % of total. Normal total cholesterol figures range from 150 to 250,<sup>5</sup> although another authority<sup>2</sup> places the lower normal as slightly less (140). The ratio of free cholesterol to the total ranges in the normal from 20 to 40%. Two patients, Nos. 7 and 12, showed significantly lower total figures, 111.8 mg. and 104.6. Both, however, showed normal ratios of esters and free cholesterol and in neither case was the ester figure below the "critical level" of 60 mg. Parenchymal liver damage is usually associated with a decline in the total cholesterol as well as the ester fraction but the decrease in the latter is relatively greater than in the total. Factors other than liver function disturbances may influence the total cholesterol and its fractions, and it is considered unwise to regard this as more than an "omen" of liver damage according to Lichtman.<sup>5</sup>

There is considerable difference of opinion as to the value of prothrombin index as test of hepatic dysfunction. Normal and above normal findings may be misleading and even subnormal values cannot be considered as evidence of true dysfunction. If values of 90 to 100% are regarded as normal, Cases 3, 7, 8, 9 and 12 were below 89% and should be regarded as subnormal. The influence of absorption of vitamin K from the gastro-intestinal tract upon the prothrombin index cannot be measured except by the injection of this substance. Whether the change in prothrombin time following such injection can be taken as an index of hepatic function is still a moot question.

Increased serum alkaline phosphatase activity has been noted in patients with active tuberculosis.<sup>2</sup> While not truly a test of hepatic function, it is almost invariably increased in clinical and experimental forms of hepatocellular jaundice. Bodansky uses a high norm of 4 units while Cantarow and Trumper<sup>2</sup> insist upon a considerably higher value, up to 11 units,

is also of interest that while 12 of the 18 cases showed values greater than 4 units, only 2 were above the higher norm of 11 units, and only 1 with a significant increase, readily explained. Quick's modified intravenous hippuric acid synthesis, considered an important test of liver function is apparently little affected in tuberculous patients. Accord-

TABLE 1.—BLOOD CHEMISTRY IN CASES OF ADVANCED TUBERCULOSIS

	Bilirubin (mg./100 cc.)	Urobilinogen (mg./24 hrs.)	Non-protein nitrogen (mg./100 cc.)	Serum protein			
				Total (gm./ 100 cc.)	Albumin (gm./ 100 cc.)	Globulin (gm./ 100 cc.)	Fibrinogen (gm./ 100 cc.)
1. B. H. . . . .	0 44	0.24	30	7.78	4.60	2.79	0.39
2. H. B. . . . .	0 53	0 26	29	7.94	4.91	2.87	0.16
3. J. D. . . . .	0 30	0.67	33	7.54	4.29	2.98	0.27
4. L. Y. . . . .	0 35	0.15	30	7.37	4.08	2.60	0.69
5. G. T. . . . .	0.43	0.09	26	8.02	4.49	2.99	0.54
6. W. H. . . . .	0.32	0.05	30	7.78	4.78	2.54	0.46
7. J. M. . . . .	0.60	0.21	25	8.13	4.32	3.31	0.50
8. W. D. . . . .	0.34	0.25	26	7.21	3.81	2.77	0.63
9. A. K. . . . .	0.59	0.13	28	7.80	4.87	2.30	0.63
10. I. K. . . . .	0.24	0.18	19	8 33	4 00	3.52	0.81
11. G. H. . . . .	0.51	2.76	30	7.82	5.16	2.03	0.63
12. M. L. . . . .	0.13	1.60	27	8 12	3.66	3.65	0.81

TABLE 2.—HEPATIC FUNCTIONAL TESTS IN CASES OF ADVANCED TUBERCULOSIS

	Cephalin cholesterol	Hippuric acid	Prothrombin index calculated as % of normal	Alkaline phosphatase (Bodansky units)	Cholesterol			
					Total (mg./ 100 cc.)	Free (mg./ 100 cc.)	Esters (mg./ 100 cc.)	Free as % of total
1. B. H. . . . .	Neg.	1.00	90 0	5 30	228 2	76 4	151.8	33.5
2. H. B. . . . .	Neg.	0 46	86 3	5 41	158 8	34 6	124.2	21.8
3. J. D. . . . .	Neg.	1 11	80 9	5.20	144.5	48.6	95.9	33.6
4. L. Y. . . . .	Neg.	1.13	88 9	6.50	236 0	74.9	161.1	31.7
5. G. T. . . . .	Neg.	1.16	112 4	2 50	136 3	41 6	94.7	30.5
6. W. H. . . . .	Neg.	1.34	89 0	4 30	143 2	38.9	104.3	27.2
7. J. M. . . . .	Neg.	1 22	86.9	6 80	111 8	37.2	74.6	33.3
8. W. D. . . . .	Neg.	1.70	85 2	12 90	150 0	57.4	92 6	38 3
9. A. K. . . . .	Neg.	1.46	76.5	7 30	197 3	62.0	135.3	31.4
10. I. K. . . . .	Neg.	1.40	118 7	6 10	189 7	54.1	135.6	28.5
11. G. H. . . . .	Neg.	0 86	90 8	28.80	209 0	62.0	147.0	29.7
12. M. L. . . . .	4+	1.09	75 0	2 50	104.6	36.4	68.2	34.8
13. G. W. . . . .	..	..	..	6.10				
14. B. W. . . . .	..	..	..	3.10				
15. M. D. . . . .	..	..	..	3.20				
16. F. B. . . . .	..	..	..	2.40				
17. N. E. . . . .	..	..	..	3.70				
18. E. K. . . . .	..	..	..	4.40				

before placing any significance in the test. There was only 1 significantly increased value in the series of 18 cases, Patient 11, with a figure of 28.8 units (Bodansky). It is interesting to note that this patient has both a far-advanced pulmonary lesion as well as progressive osseous involvement. This latter destructive process could very well explain the high values obtained. It

ing to Quick, any urinary output of less than 0.7 gm. of benzoic acid as hippuric acid in the 1 hour urine specimen indicates some degree of impairment of hepatic function. In only 1 case (No. 2) was the reported value subnormal, 0.46 gm. The same negative results were found in Hanger's cephalin cholesterol flocculation test using Difco unripened cephalin as



advised by Mateer *et al.*<sup>5</sup> Case 12 showed a 4+ reaction while all the others were negative.

Of all the studies done in this series, the bromsulphalein test is the most important in the diagnosis of disturbance of the excretory function of the liver. By throwing a large excretory load upon the liver, marginal impairment of function may be detected. Diffuse disease of the liver without obstruction supposedly is best directed with this method. The modified

appearance of the dye after injection of 5 mg. of bromsulphalein per kg."

Table 3 shows the results of the 5 mg. test in 17 patients using the 45 minute period. Seven cases, Nos. 2, 6, 7, 8, 10, 11, 12 and 15, showed retention of the dye.

**Discussion.** In the study of hepatic function, the choice of tests is difficult because of the large number as well as the many conflicting claims made for each. It has been demonstrated by many workers that there is no constant correla-

TABLE 3.—SERIAL BROMSULPHALEIN TEST IN FAR-ADVANCED TUBERCULOSIS  
% retention measured at 5 minute intervals after injection

	5	10	15	20	25	30	35	40	45
1. B. H. . . . .	85	20	8	4	QNS	2	0	0	0
2. H. B. . . . .	60	30	20	15	10	7	7	7	5
3. J. D. . . . .	70	35	15	7	4	0	0	0	0
4. L. Y. . . . .	65	25	15	7	6	5	0	0	0
5. G. T. . . . .	65	25	15	7	2	12	0	0	0
6. W. H. . . . .	80	35	20	10	8	7	6	6	4
7. J. M. . . . .	85	25	15	10	8	6	5	4	2
8. W. D. . . . .	70	40	20	15	12	10	8	8	7
9. A. K. . . . .	90	35	20	10	7	0	0	0	0
10. I. K. . . . .	60	20	10	5	2	0	0	0	0
11. G. H. . . . .	90	40	30	20	20	QNS	QNS	20	20
12. M. L. . . . .	..	..	..	..	..	..	7	..	7
13. G. W. . . . .	55	40	25	20	20	18	18	18	18
14. B. W. . . . .	55	20	10	5	3	0	0	0	0
15. M. D. . . . .	55	25	15	7	5	0	0	0	0
16. N. E. . . . .	90	55	35	20	15	10	7	5	4
17. E. K. . . . .	45	22	12	7	6	4	0	0	0

TABLE 4.—A STUDY OF ABNORMAL VALUES IN HEPATIC FUNCTION

	Hippuric acid	Cephalin cholesterol	Phosphatase	Cholesterol		Bromsulphalein 45 min.)
				Total	Esters	
2. H. B. . . . .	0.46	Neg.	5.41	158.8	124.2	5
6. W. H. . . . .	1.34	Neg.	4.30	143.2	104.3	4
7. J. M. . . . .	1.22	Neg.	6.80	111.8	74.6	2
8. W. D. . . . .	1.70	Neg.	12.9	150.0	92.6	7
11. G. H. . . . .	0.86	Neg.	28.8	209.0	147.0	20
12. M. L. . . . .	1.09	4+	2.5	104.6	68.2	7
13. G. W. . . . .	..	..	6.1	..	..	18
16. N. E. . . . .	..	..	3.7	..	..	4

test using 5 mg. per kg. dose was applied taking 5 minute serial samples of blood up to 45 minutes. Mateer *et al.*<sup>6</sup> have carefully studied the entire problem of normal and abnormal results and definitely state that in a study of normal young people, "the dye had completely disappeared from controls in 30 minutes, in 86% in 35 minutes, in 96% in 40 minutes and in 100% . . . in 45 minutes. The 45 minute period has been adopted therefore as the normal standard for complete dis-

tion between results obtained from different tests in the same individual. The specific objections levied against function studies may be stated as (1) the tremendous reserve power of the liver; (2) the numerous functions of the liver so that any one test is insufficient to judge the function of the whole; and (3) the tests lack sensitivity.<sup>5</sup> These objections have all been answered by Lichtman who also states "It has long been recognized that

there is no correlation between structure and function of the liver cells."

Although the actual pathologic process in the liver of tuberculous patients usually is not a striking one, one may expect to find functional abnormalities in such patients with a toxic wasting illness affecting all of the body so profoundly. It is therefore not unexpected that patients with far-advanced long-standing tuberculosis would show changes in one or another of the functional studies done.

A recapitulation of the abnormal findings in Table 4 show that the only patient with the best correlation of abnormal function was M. L. (No. 12) with a 4+ cephalin cholesterol flocculation test, a low cholesterol and retention of bromsulphalein. This patient had extensive amyloidosis with a 100% retention of Congo red, an enlarged liver and spleen, and albuminuria. The only other amyloidosis patient in this series, G. H. (No. 11), showed a high phosphatase activity explained possibly by extensive osseous tuberculosis, and a considerable brom-

sulphalein retention, but with otherwise normal findings.

A careful study of Table 4 shows that there is no uniform correlation of findings, with hippuric acid synthesis and cephalin cholesterol flocculation showing the least positive, while the bromsulphalein excretion gave the greatest number of positive results.

**Conclusions.** 1. Hepatic function studies were done in cases of far-advanced pulmonary tuberculosis.

2. In addition to static values for NPN, serum proteins, total cholesterol and cholesterol partition, prothrombin phosphatase bilirubin, urobilinogen, other studies were done such as Hanger's cephalin cholesterol flocculation test, hippuric acid synthesis and the 5 mg. serial bromsulphalein test.

3. Hepatic dysfunction was demonstrated in a large percentage of cases.

4. The serial bromsulphalein test showed the greatest number of positive results.

5. The most outstanding abnormalities were found in 2 patients with complicating amyloidosis.

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## THE ESOPHAGEAL VARIX

## A REPORT OF ONE HUNDRED AND FIFTEEN CASES

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ESOPHAGEAL varices have always been a dreaded complication of patients with diseases causing increased pressure in the portal vein. These varices, although often silent, insidious and symptomless in development, frequently rupture suddenly and control of the hemorrhage is usually unsuccessful. Recent advances in the early treatment of this disease give some hope of changing its relentless progress toward eventual rupture and exsanguination to possible cure and eradication of the varix. An understanding of the pathogenesis of this condition, its incidence, and the utilization of the means of early diagnosis and prompt institution of treatment are most important in making this possible.

**PATHOGENESIS.** Kegaries<sup>6</sup> demonstrated that a communication exists between the portal and caval system by way of the esophageal veins: they have at one end anastomoses with the splenic and coronary veins of the portal system and at the other with the azygos, intercostal and diaphragmatic veins of the systemic circulation. The absence of valves in the coronary vein makes a reversal of direction of blood flow possible, so that in portal hypertension the blood tends to dam back and enter the systemic circulation by way of the esophageal anastomoses. The damming back of blood from the portal system through the coronary vein overtaxes the capacity of the esophageal veins and in this manner varicosities begin. Other factors which contribute to their development are the poor support which the esophageal veins receive by the loose connective tissue in the esophageal submucosa and the sucking action of the diaphragm during respiration. The anatomic location of esophageal varices constantly ex-

poses them to trauma which may lead to fatal bleeding.

The tributaries of the portal vein constitute the venous drainage from the gastrointestinal tract, the gall bladder, the pancreas and the spleen. Portal hypertension may take place as result of block of this venous return occurring within the liver as in cirrhosis, or extrahepatically along part or all of the portal system. Whipple<sup>15</sup> speaking of portal hypertension has said: "If there is a high retention of the bromsulphathalein in the blood 30 minutes after intravenous injection, if the hippuric acid test is positive, if there is a reversal of the albumin globulin ratio or if the cephalin flocculation test is positive, the presence of a cirrhosis with intrahepatic portal block is fairly certain. On the other hand, if these tests are negative it is safe to assume that block is extrahepatic." Extrahepatic block is most commonly due to chronic congestive splenomegaly (Banti's syndrome or to splenic vein thrombosis.

**DIAGNOSIS.** Early diagnosis of the esophageal varix has always been exceedingly difficult and usually the disease is unrecognized until a patient with cirrhosis of the liver or splenomegaly has 1 or more episodes of hematemesis. Frequently it is not suspected and is found at the autopsy table or by coroners investigating causes of sudden death. In 1925 Chevalier Jackson<sup>5</sup> suggested esophagoscopy as an aid in diagnosis, but this method has not been widely used for fear of producing fatal hemorrhage by abrasion of the varices during instrumentation. With careful use, however, esophagoscopy is justified and there is minimal risk. Varices are usually demonstrated with ease by this

procedure and sometimes they are so large that they appear to occlude the lumen of the esophagus (Fig. 1).

In 1928 Wolf<sup>17</sup> first demonstrated esophageal varices by the use of Roentgen rays

To demonstrate these one must coat the esophageal lumen with a thin layer of barium mixture. A thick mixture of barium is usually not satisfactory. The varices, as a rule, are smaller when the

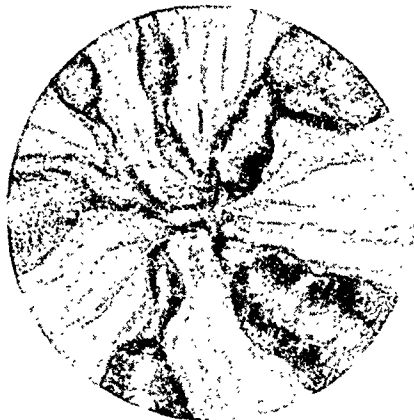


FIG. 1.—Esophageal varices as seen through an esophagoscope.



FIG. 2.—Roentgen ray visualization of esophageal varices with opaque suspension in 2 patients.

and these observations have been confirmed many times. The principle of Roentgen ray visualization depends upon the bulging of the dilated veins into the lumen of the esophagus causing an uneven worm-like appearance along the inner surface (Fig. 2).

patient is in the upright position and the examination is best performed when the patient is horizontal and "bearing down." Sometimes they are demonstrated at fluoroscopy but usually "spot" films are necessary. One must remember that var-

ices are compressible anatomic formations and various factors such as peristalsis, position and respiration may influence their filling.

In the differential diagnosis of the Roentgen ray picture, according to Plotz and Reich,<sup>11</sup> one should rule out food particles, polyps, new growths and cardiospasm. Repeat examinations after thorough evacuation of food will usually eliminate the possibility of food particles. Polyps may be ruled out because in this condition there is a rapid passage of barium and an absence of obstruction in proportion to the degree of protrusion. It is important to differentiate new growths of the esophagus and these often are ruled out by the softness of the esophageal wall and its elasticity which appears unimpaired. Esophagoscopy is sometimes necessary. In cardiospasm there is usually a smooth esophageal wall unlike that when varices are present.

Careful roentgenographic study of the esophagus is indicated in all persons who show evidence of portal hypertension. It is to be remembered that negative Roentgen ray or fluoroscopic findings do not rule out the possibility of varices and esophagoscopy may be necessary.

There is some question as to the advisability of these procedures in patients who have already had episodes of hematemesis and individual consideration must be given each case. When there is no evidence or history of recent bleeding, Roentgen ray examination and esophagoscopy are unlikely to promote new hemorrhages.

**INCIDENCE.** There is considerable variation in the literature as to the incidence of esophageal varices and the frequency of hemorrhage from them, whether fatal or not. In 1900, Preble,<sup>12</sup> in a study of 60 cases of fatal gastro-intestinal hemorrhage occurring in patients with cirrhosis of the liver, found esophageal varices in 80% and in half of these was able to demonstrate rupture of the varix. McIndoe<sup>8</sup> reporting 26 deaths due to cirrhosis found ruptured esophageal varices in 50% of them. Rivers and Wilbur<sup>13</sup> reviewed 668

patients who came to the Mayo Clinic with a primary complaint of hematemesis and found that bleeding was attributable in 5.1% of the cases to cirrhosis of the liver or splenic anemia.

In this study 115 cases of esophageal varices occurring since 1919 at the San Francisco City and County Hospital (Department of Public Health, City of San Francisco) are reported. Of these cases, 84 had proven esophageal varices by Roentgen ray, esophagoscopy, or autopsy. The remaining 31 were so diagnosed clinically because of strongly suggestive history, physical and laboratory findings and clinical course. It should be noted that difficulties in reporting statistics of this disease are especially great because patients are frequently admitted in shock and die before an adequate history can be obtained and the diagnosis is made at the autopsy table; whereas in other cases where a history, physical examination, laboratory studies and course all indicate cirrhosis of the liver or chronic congestive splenomegaly, perhaps with esophageal varices, an autopsy is not obtained or the varices are not demonstrated at postmortem examination. The 31 clinically diagnosed cases of esophageal varices were of this group. The inability to demonstrate esophageal varices at autopsy is well known. It is generally conceded that many more could be demonstrated if contrast media were injected to detect them but this procedure is not the general practice at this hospital. Consequently at best one is only able to acquire the approximate incidence of esophageal varices and the frequency of related fatal hemorrhage.

It is of interest to note (Table 1) that 61% of these patients entered the hospital because of hematemesis and 84% of these (or 51% of the total group) died of hemorrhage. Only 18% of those studied gave a history of previous episodes of hematemesis, which gives a rather ominous outlook for the patient with esophageal varices when he first vomits blood. There was a history of excessive alcoholism in 61% and in 80% cirrhosis of the liver was

either diagnosed or found at autopsy (Table 2). Other causes of esophageal varices resulting from portal hypertension included chronic congestive splenomegaly, gumma of the liver, portal vein thrombosis and tumors of the liver. The age of the patient varied from 26 to 80 years, the average of the whole group being 50.

tion or spider angiomas in the cases studied (Table 3). The incidence of peripheral neuritis was surprisingly low in a group composed so largely of alcoholics.

At best, then, one can say that esophageal varices are a frequent complication of portal hypertension and it is with just cause that both patient and doctor await

TABLE 1.—MORTALITY OF PATIENTS WHO ENTERED COMPLAINING OF HEMATEMESIS AND THE INCIDENCE OF PREVIOUS HEMORRHAGES IN THE 115 CASES OF ESOPHAGEAL VARICES STUDIED

	Group A (84 proven cases)	Group B (31 clinically diagnosed cases)	Total (115 cases both groups)
Presenting complaint: hematemesis . . . . .	♂ 32 ♀ 24 — 56 (66%)	♂ 10 ♀ 4 — 14 (45%)	Both sexes 70 (61%)
Previous history of hematemesis . . . . .	♂ 11 ♀ 4 — 15 (18%)	♂ 9 ♀ 1 — 10 (32%)	Both sexes 25 (22%)
Died of hemorrhage . . . . .	♂ 31 ♀ 18 — 49 (59%)	♂ 7 ♀ 3 — 10 (32%)	Both sexes 59 (51%)

*Mortality of total group of patients who entered with presenting complaints of hematemesis: 59 of 70 (84%).*

TABLE 2.—AVERAGE AGE, INCIDENCE OF CIRRHOSIS AND HISTORY OF ALCOHOLISM IN 115 CASES OF ESOPHAGEAL VARICES STUDIED

	Group A (84 proven cases)	Group B (31 cases clinically diagnosed)	Total (115 cases)
Average age . . . . .	♂ 50 ♀ 47 — 63 (75%)	♂ 54 ♀ 49 — 29 (94%)	50 years
Incidence of cirrhosis . . . . .	♂ 40 ♀ 23 — 63 (75%)	♂ 20 ♀ 9 — 29 (94%)	92 (80%)
History of alcoholism . . . . .	♂ 26 ♀ 20 — 46 (55%)	♂ 16 ♀ 8 — 24 (80%)	70 (61%)

The vast majority of the patients had an unexpected sudden onset of hemorrhage usually unrelated to stress, cough or eating. In 4 the bleeding occurred while the patients were asleep and they woke up with feelings of nausea and vomited blood. Five of the patients noted the onset of their hematemesis following a blow to their abdomen or thorax and several more associated their onset with coughing. There seemed to be no relation between the occurrences of varices and the presence of an enlarged liver or spleen, jaundice, ascites, edema, collateral nervous circula-

TABLE 3.—OCCURRENCE OF MISCELLANEOUS PHYSICAL FINDINGS OF THE 115 PATIENTS WITH ESOPHAGEAL VARICES

	No. cases
Enlarged liver . . . . .	81
Jaundice . . . . .	38
Ascites . . . . .	37
Edema . . . . .	18
Palpable spleen . . . . .	20
Collateral venous circulation . . . . .	24
Peripheral neuritis . . . . .	8
Spider angiomas . . . . .	23

with alarm and fear their development and eventual rupture. Such a poor prognosis should be sufficient reason for a relentless search for a method of eradica-

tion and treatment of this situation, generally thought hopeless.

**TREATMENT.** Until quite recently the treatment of esophageal varices has been very discouraging. Medical treatment has been more directed at the underlying condition. In patients with cirrhosis of the liver diets high in protein, carbohydrate and vitamins and the use of liver concentrates have been of some value in improving liver function, and this probably reduces the likelihood of varices developing. Mercurial diuretics have been only palliative. Drenckhahn<sup>3</sup> suggested that blood with a lower viscosity might pass more easily through the liver since it presented less obstruction and in this way the portal pressure would be reduced. He found that some patients who had frequently bleeding esophageal varices bled when the total red blood count was close to normal. The blood at this time is considerably more viscid than when there are about half the normal number of red blood cells present. He reported the successful treatment of 1 patient whose blood he kept at a low viscosity by repeated venesections. This method, however, has not received general use.

Treatment of the reported cases of this paper was only palliative and was entirely unsatisfactory. All of the patients were treated for shock, sedated, kept at bed rest, and dietary precautions were observed. About half were given plasma or whole blood transfusions during the bleeding phase. Some authorities maintain that the increase in blood volume which occurs during transfusion is unwise during a hemorrhage in that the tear in the vascular wall is less likely to close at this time. However, we noticed no significant difference in the group who received transfusions.

More favorable results have been obtained by surgical intervention. Removal of the spleen is perhaps the most common surgical procedure although some observers report recurrences of hemorrhages from esophageal varices following splenectomy.<sup>1</sup> Omentopexy has been done to

establish collateral circulation around the liver through the veins of the peritoneum and the abdominal wall, especially through the superior epigastric veins. Interrupting the flow of blood to the esophageal veins by ligation of the coronary vein with or without splenectomy as described by Rowntree, Walters and McIndoe<sup>14</sup> produced favorable results in some cases. Moersch in 1941<sup>7</sup> reported the injection of sclerosing substances into the varices under direct vision with the use of the esophagoscope but thought this method should follow splenectomy. Patterson and Rouse<sup>9</sup> reported in 1946 injecting the esophageal varices of 8 patients with 5% sodium morrhuate. Two later died from bleeding varices. It is interesting that they treated successfully by injection the bleeding varices of 1 patient while he was in shock from loss of blood and were able to stop the bleeding. The success of this treatment, although heroic in nature, should be borne in mind when one is confronted with similar patients who are moribund from bleeding esophageal varices. Neither vein ligation nor the injection treatment *per se* of the esophageal varices is physiologically sound, for unless other methods are used to reduce the portal hypertension the varices most likely will recur.

A more physiologic approach to the treatment of the esophageal varix is that of lowering the pressure in the portal vein which in turn will decrease the pressure in the esophageal veins. This can be done by anastomosing the portal and caval circulations. In 1877 Eck<sup>4</sup> first suggested this as a method of sidetracking the venous return in obstruction of the portal vein. The Eck fistula procedure has been tried occasionally since then, but the high operative mortality discouraged its general use. The recent developments in vascular surgery has renewed the interest in this procedure. In 1946 Blakemore and Whipple<sup>1,16</sup> reported portocaval anastomotic procedures on 14 patients, 4 with extrahepatic portal obstruction and 10 with intrahepatic obstruction due to portal

cirrhosis. There were 2 postoperative deaths, both among the cirrhosis group, but the remainder were considerably improved, and had little or no gastro-intestinal bleeding postoperatively. Several had marked reduction in ascites.

Blalock<sup>2</sup> recently has supported the portocaval shunt operation in the treatment of ascites and gastro-intestinal bleeding as being the most sound of any of the methods of treatment so far advocated and has done this procedure on selected cases. The technical skill required for the operation is considerable and its success depends upon the portocaval junction not breaking down and remaining patent enough for an appreciable amount of blood to by-pass the liver.

It is hoped that further experience accompanied by good results will popularize this first physiologic attack on a serious problem so far unsolved.

**Summary.** Of 115 patients with esophageal varices reported here, 70% entered the hospital with the presenting complaint of hematemesis and 84% of these died of hemorrhage shortly after admission. A previous history of hematemesis was elicited in 22%. Other factors including the incidence of cirrhosis, alcoholism, age and physical findings of these patients are presented. The pathogenesis and methods of diagnosis of esophageal varices are described and the various forms of treatment including the recent work on portocaval anastomoses are discussed.

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# PROGRESS OF MEDICAL SCIENCE

## DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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### THE ACTION OF PENICILLIN ON *TREPONEMA PALLIDUM*\*

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ALTHOUGH it is just a little more than 4 years since Mahoney, Arnold and Harris<sup>34</sup> demonstrated that penicillin was effective treatment for early syphilis in rabbits and man, a voluminous literature has appeared on the value and limitations as well as possible mechanism of this action. Since the first trials of penicillin in syphilotherapy, many new developments have conditioned the degree of this antispirechetel effect. Commercial penicillin has been shown to be a mixture of several types, named in this country F, G, X and K, each, as well as the commercial product, with its own pharmacologic action against spirochetes *in vitro* and *in vivo*; impurities in the original mixtures have an activity against spirochetes; the individual penicillin types in the crystalline state act differently from mixtures containing varying amounts of the various types, and lately penicillin has been synthesized, a development which as yet has yielded no opportunity for those interested in syphilotherapy to take advantage of. It has also been demonstrated that penicillin has similar potency against other spirochetel infections such as relaps-

ing fever,<sup>16d,24c,47,51</sup> yaws,<sup>14,32,53,62</sup> Weil's disease,<sup>1,2,24b</sup> Vincent's infection,<sup>37,48,50</sup> and rat-bite fever.<sup>24c,27,33,46</sup> Employment of penicillin in these diseases may yield rapid methods for determining the value of various penicillins against syphilis. In addition to the group specific action of penicillin against various spirochetes, it apparently has a varied effectiveness against virulent *Treponema pallidum* as contrasted with avirulent cultured organisms of so-called Reiter, Nichols and Kazan strains. In spite of careful evaluation of the many factors defining the mode of action of penicillin on spirochetes, especially *T. pallidum*, the exact mechanism and site of action are little understood. However, because of the industry of a group of laboratory investigators (Eagle, Mahoney, Chesney, Magnuson, Fleming, Rosahn, Levaditi, Carpenter, Rake and their associates), sufficient data on various aspects of the problem of the effect of penicillin on *T. pallidum* are available for review. We intend to discuss this material under the following heads: The activity of penicillin against *T. pallidum in vitro*, including commercial penicillins F, G, X and K;

\* *Treponema pallidum* and *Spirocheta pallida* are used interchangeably as the designation for the organism alleged to cause syphilis.

the effect of penicillin in experimental rabbit syphilis, including the effectiveness of commercial penicillin, penicillins F, G, X and K and impurities of commercial penicillin; resistance to penicillin; and the mode of action of penicillin on *T. pallidum*.

At present, information on the various topics listed above is limited in many respects and, as is usually the case, results from *in vivo* animal studies and *in vitro* experiments cannot be directly applied to the problem of human infection with syphilis. Although there is in general a rough parallelism between the *in vitro* activity of penicillin against various organisms and its clinical use in infections caused by them, various factors in animals and man, variations in absorption, excretion, the presence of inhibitors and the complex nature of the difficult to cure disease, syphilis, etc., may cause this relationship to break down in specific instances. Another *desideratum* for the future study of the effects of penicillins on *T. pallidum* is a standardized preparation with dosage in milligrams and not in terms of potency against a particular organism unrelated to that alleged to cause syphilis. In this connection, Moore<sup>39b</sup> has aptly stated that "To express dosage in syphilis, caused by the *Treponeme pallidum*, in terms of staphylococcus units determined *in vitro* is, to say the least, a *non sequitur*."

"What appears to be needed, therefore, now that the honeymoon is over, is a systematic and painstaking study of the following:

"1. Exact definition of the basic chemical structure of penicillin, and if possible, its synthesis.

"2. Separation from commercial penicillin of its various species, and their preparation in pure crystalline form.

"3. The expression of dosage in gravimetric forms, i. e., milligrams in place of units.

"4. The chemical synthesis of new modified penicillin.

"5. The rate of absorption and excretion of each penicillin as prepared in crystalline form.

"6. The effectiveness, both *in vitro* and *in vivo*, of each crystalline penicillin against various bacteria.

"7. Toxicologic, pharmacologic, and therapeutic study of each crystalline penicillin."

THE ACTION OF PENICILLIN ON *T. PALLIDUM* IN VITRO. In 1944, Eagle and Musselman<sup>17a,b</sup> made an extensive study of the spirocheticidal action of commercial penicillin *in vitro* and its temperature coefficient. In view of the fact that pathogenic spirochetes have as yet not been cultured, recourse was had to non-pathogenic strains, especially the so-called Reiter strain. Penicillin was found to be actively spirocheticidal *in vitro* (direct spirocheticidal effect) against the Reiter, Kazan, Nichols and Noguchi strains of *T. pallidum* and a strain of mouth spirochetes. The threshold concentration was 0.01 unit per cc. (1:160,000,000 penicillin). The rate and degree of action increase with the concentration of penicillin up to a level of 0.1 to 0.25 unit per cc., which rendered more than 99 % of the organisms non-viable within 12 hours. Higher concentrations did not appreciably accelerate the effect. Within limits ( $4 \times 10^4$ – $10^7$  organisms per cc.) the initial rate at which the spirochetes were killed was not affected by this number but the amount of penicillin required to sterilize suspensions of varying density varied to a large extent with the initial number of organisms. It was found that the organisms remained actively motile for a period of 8 to 24 hours after they had been rendered non-viable by the action of penicillin. Higher concentrations (500 units of penicillin per cc. or approximately 10,000 times an effectively spirocheticidal concentration) did not accelerate that delayed immobilization. Thus, although penicillin rapidly renders organisms non-viable, the metabolic system affected is not immediately essential to the life of the cell, and the motility and presumably other vital functions remain unaffected for a significant number of hours. The rate at which organisms were killed by penicillin increased with tem-

perature in the range of 8° to 40° C. Of an original inoculum of 10<sup>6</sup> spirochetes per cc. exposed to penicillin, the percentage of organisms surviving after 24 hours was 100 at 80° C.; 10 at 22° to 23° C.; 1 at 32° to 33° C.; and only 0.02 at 30° to 40° C. These results were independent of the concentration of penicillin in the range of 0.25 to 250 units per cc. They suggest that the combined use of penicillin with fever in the treatment of syphilis may be more effective than either one alone. Lee and Foley<sup>28</sup> showed *in vitro* that with other organisms (not spirochetes) within the range of 37° to 42° C., the action of penicillin is enhanced by increased temperature. They found that the action is furthermore far greater on organisms undergoing rapid rate of growth. At high temperatures the drug kills organisms that are not undergoing growth, an effect which would otherwise require excessively high concentrations of the drug. The same synergistic action of fever and penicillin has been noted by Hoyt, Pratt and Levine.<sup>25</sup> Dunham, Hamre, McKee and Rake,<sup>12</sup> employing the technique of Eagle,<sup>15d</sup> using Nichols strain of *Spirochæta pallida*, obtained from rabbit testes in the stage of acute orchitis, found penicillin to be spirocheticidal when relatively high concentrations (800 to 1600 Oxford units per 0.8 ml.) were used. Bessemans and Derom,<sup>5c</sup> confirming an earlier experience<sup>5a</sup> and using fragments made of about 1 c.mm. of testicular syphiloma of the rabbit rich in spirochetes and physiologic emulsions homogenized by gentle centrifugation so that there were about 2 to 3 metile treponemas per field, found that after 3 hours of action at 37° C. penicillin was treponemicidal *in vitro* in a concentration of 10,000 units per cc. A concentration of 1000 units produced partial action as judged by the retarded appearance of lesions in rabbits' testes. The state of the pathogenic material did not influence the results; the penicillin seemed well diffused in the tissues. Moore<sup>33b</sup> cites unpublished work of Eagle to the effect that exposure of pathogenic treponemas to the

commercial penicillin, in a concentration of 64 units per cc. at 37° C. for periods of from 8 to 24 hours, did not impair their infectiousness. "This paradoxical finding, inconsistent either with the direct spirocheticidal action of penicillin on cultured spirochetes, or its effect on pathogenic *Treponema pallidum in vivo*, has not yet been explained."

The effect of penicillin *in vitro* on spirochetal and other microbic morphology, observed by darkfield on the electron microscope, has been reported by various investigators. Details and the possible significance of their findings will be discussed below.

Commercial penicillin contains at least 4 molecular species (F, G, X and K in this country, and penicillin I, II, III and K respectively in Great Britain). They differ from each other in the nature of the side group attached to a common nuclear structure. These penicillins are known to vary in their bactericidal activity *in vitro* (Ory *et al.*,<sup>44</sup> Veldee *et al.*,<sup>55</sup> Welch *et al.*,<sup>61</sup> Libby *et al.*<sup>31</sup>) Compared with penicillin G, rated as 100, the relative activities per mg. of penicillin F, G, K and X against *Staphylococcus aureus* are reported to be 90, 100, 140 and 55 respectively (1550, 1667, 2300 and 900 units/mg.). Eagle and Musselman<sup>17c</sup> found that crystalline specimens of F, G, K and X have a relative gravimetric activity *in vitro* of 82, 100, 120 and 140 against the C-203 strain hemolytic streptococcus, and 53, 100, 75 and 50 respectively, against a cultured strain of *Spir. pallida* (Reiter).

In addition to the 4 forms of penicillin in the commercial product, there are different amounts of other substances of unknown nature. As was the case with the arsenicals, purification of penicillin has resulted in a somewhat lessened antispirochetal activity. This is suggested by the larger and larger dosages of penicillin salts needed for the control of clinical syphilis. The possibility that these impurities may have antispirochetal properties is suggested by the observations of Dunham and Rake<sup>12</sup> who found that while partially

purified penicillin immobilizes *T. pallidum* *in vitro* (Dunham, Hamre, McKee and Rake), crystalline penicillin G has very little or no effect on the motility of *T. pallidum* when the latter is exposed to 8800 u./ml. for 2 hours *in vitro*. Under the same conditions, a solution containing 2200 u./ml. of the least pure penicillin preparation employed in their studies, immobilizes all of the spirochetes. A substance in partially purified penicillin that immobilizes spirochetes can be concentrated by adsorption on alumina and recovered by elution. The concentration of the substance in partially purified penicillin that is active against spirochetes *in vitro* is only slightly, if at all, reduced by incubation at 37° C. in the presence of a weak solution of penicillinase over a period of 11 days, conditions under which a large proportion of the penicillin present is inactivated.

Dunham and her associates concluded that the immobilization of spirochetes *in vitro* by partially purified penicillin is due to one or more of the impurities present. No marked degree of immobilization of spirochetes is produced by solutions containing 3.5 mg./ml. of penillic acid or 30 mg./ml. of a product of the hydrolysis of pure penicillin G. They found in addition that spirochetes exposed to 1100 u./ml. of certain partially purified preparations of penicillin are non-infectious for rabbits when injected intratesticularly, although many of the organisms were still motile at the time of injection. Spirochetes similarly exposed to 8800 u./ml. of crystalline penicillin G (8 times as much) produces orchitis in rabbits. The comparative findings of these authors in experimental syphilis in rabbits will be discussed later.

**THE ACTION OF PENICILLIN ON *T. PALLIDUM* IN VIVO.\*** As noted previously, the results of *in vitro* studies of the antispirechetel action of penicillin can be referred

only in a general way to the effects of the class of preparations *in vivo* (animals and man). Still, the efforts of the group of laboratory workers noted above have yielded information which may lead to a better understanding of the therapeutic problem in man.

Shortly after Mahoney, Arnold and Harris<sup>34</sup> showed that penicillin was active against syphilis in animal and man, other studies began to appear. Several of these (Selbie and Simon,<sup>49</sup> Ercoli and Lafferty,<sup>48</sup> Raiziss<sup>45</sup>) dealing with a small number of animals (less than 10) indicated that penicillin was of little or no value in experimental rabbit syphilis. For example, Ercoli and Lafferty found that a single intravenous dose of penicillin sodium—33,000 to 47,000 u./kg. or 16,000 u./kg. if the drug were given over a period of 72 hours in doses of approximately 4000 u./kg.—was required to produce disappearance of *T. pallidum* in experimental rabbit syphilis. Lymph node transfer in 4 rabbits, however, indicated that the highest doses used (132,000 to 282,000 u./kg.) did not sterilize the rabbits. Selbie and Simon likewise found that 45,000 u./kg. when given to rabbits in 3 equally divided doses at intervals of 3 hours, caused the disappearance of organisms within 24 hours, as determined by the direct examination of testicular lesions. Organisms, however, reappeared in the majority of the syphilmata in from 30 to 45 days after treatment. In view of the clinical experience and other later studies, these early investigators did not take into account the factor of time-dosage relationships necessary for cure with syphilis. (McDermott<sup>36</sup> and his colleagues found, based on available *in vitro* and *in vivo* data, that "it would seem that a serum penicillin concentration of 0.078 unit per cc. is probably well above the 'effective level' for the spirochete.") In addition, their results are clear demonstration of the unreliability

\* A number of studies, not yet in print, have been publically presented in a symposium, Recent Advances in the Investigation of Venereal Diseases, in Washington, D. C., on April 17, 1947, under the Syphilis Study Section of the National Institute of Health. Since these data are not officially available, they are not included in this review.

of disappearance of spirochetes from lesions as evidence of cure (Beerman<sup>4</sup>). Even small doses of penicillin will readily cause surface sterilization in clinical syphilotherapy (Binkley and Kile;<sup>5</sup> Moore and co-workers<sup>40</sup>). Dunham, Hamre, McKee and Rake in 1944<sup>12</sup> furthermore found that inadequate dosage in rabbit syphilis resulted in the production of a more resistant strain of *T. pallidum*. Bessemans and Derom,<sup>55</sup> on the other hand, reported that rabbits and mice were completely sterilized when given relatively large doses of penicillin, namely, a total dose of 320,000 Oxford units (5000 units injected intramuscularly at 3 hour intervals in 8 days) for the rabbits and 12,800 units for 8 days and 18,000 units in 1.5 days for the mice.

In a later communication, Bessemans and Derom<sup>56</sup> reported new results of penicillin therapy of rabbits and mice. They observed that complete sterilization as measured by tissue transfer occurred in mice with a total dose of 800,000 u./kg. in 8 days at the onset of the infection, and 1,200,000 u./kg. in 11 days in the old cases. In the rabbit the good results were obtained when the treatment was given in doses totalling 100,000 u./kg. in 8 days or of 250,000 u./kg. in 19 days, either as injection in physiologic saline every 3 hours or every 12 hours as an emulsion in oil (according to the procedure of Romansky and Rittman). Earlier (1944) Levaditi and Vaisman<sup>30</sup> stated from their experiences, in preliminary studies, that penicillin injected either locally or intravenously in variable numbers of multiple doses but with total dosage of 7500, 10,000 and 80,000 Oxford units, caused rapid disappearance of spirochetes and healing of lesions in rabbit syphilis (Gand strain) in a short time. Curative action clinically speaking was certain. The question of complete sterilization by penicillin had not been determined. In mice with asymptomatic infections, 750,000 Oxford u./kg. body weight were needed to cause complete sterilization. In 1945 they demonstrated that penicillin given intra-

venously in rabbits in total doses ranging between 500 and 40,000 u./kg. at 1 to 3 injections daily, caused a rapid curative effect from the standpoint of disappearance of spirochetes and lesion healing. However, when given intramuscularly in total mass of 40,000 Oxford u./kg. in 20 doses in 4 to 5 days, they noted that penicillin caused not only rapid disappearance of spirochetes and clearing of the lesions, but complete sterilization of the animal's syphilis. Total dosage and rhythm of the injections seem to play an important rôle in the results obtained. In addition, these investigators noted that penicillin given intramuscularly in dosage of 6000 to 40,000 Oxford u./kg. caused rapid disappearance of spirochetes from rabbit syphilomas as determined by darkfield, but silver stains for tissue spirochetes were positive and spirochetes were present in great numbers in the lesions. Certain of them showed involution forms. the loss of pathogenic growth preceding total resorption of the organisms resembling the effects of bismuth and arsenicals.

Fleming and Wolf<sup>21</sup> employed an aqueous solution of a relatively crude sodium penicillin (2930 per mg.); 25% penicillin X in early and late rabbit syphilis (duration 6 weeks and 6 months after infection respectively) in a schedule of intramuscular injections every 3 hours day and night for 4 days (32 injections) in 5 total dosages ranging from 500 to 80,000 u./kg. Using Eagle's criteria of cure and 10 rabbits for each of the schedules, they found that the  $CD_{50}$  (dose curing 50%) in early syphilis was 1100 u./kg.; the  $CD_{95}$  dose (curing about 95%) was 2000 units. In late syphilis the corresponding figures were approximately 500 and 2000 u./kg. These data indicate that late rabbit syphilis is as curable as the early infection and perhaps with even a somewhat smaller dose. Moore<sup>32</sup> cites experimental data of Arnold (unpublished) which suggest that in the rabbit, at any rate, cure of syphilis with penicillin can be accomplished in a short time (12 hours) by enormously increasing the total dose, to

perhaps 400,000 u./kg., the equivalent of 28,000,000 units in a 70 kg. man. Experiments of this sort have been carried out by Schwemlein and his associates who have treated 162 patients with primary or secondary syphilis by continuous intravenous drip of from 10,000,000 to 25,000,000 units of penicillin over a 24 hour period. Their clinical results have not as yet been published.

Not only is penicillin curative in 3 days in rabbit syphilis but Arnold, Mahoney and Cutler<sup>2a</sup> have demonstrated that rabbits with acute syphilis given adequate penicillin therapy were reinfected 10 days after treatment was completed. Untreated rabbits with acute syphilis reinoculated with an homologous strain of spirochetes at the same time period as the treated animals did not develop clinical evidence of reinfection.\*

From this listing of variable results of penicillin therapy in rabbits and mice, mostly favorable, one turns to the illuminating and brilliant studies of Eagle and his co-workers. Eagle has recognized the variable factors which have to be studied in order to bring order out of the chaos of penicillin therapy. Because these variable factors can be controlled in animals (especially the rabbit) with more certainty than in man, the experimental animal is a better subject for study than man. Moore<sup>39b</sup> has clearly summarized the manifold variables involved as follows: "As to commercial penicillin used alone, and injected intramuscularly in aqueous solution, these variables are the number of injections, their frequency and the total amount of the penicillin administered. Equally important is a study of absorption delaying methods (e. g., calcium penicillin in peanut oil-beeswax) with the adjuvant use of arsenic, bismuth or fever. Of still greater fundamental importance is a study of penicillin species and impurities present in commercial penicillin, to determine which of the several components is most, or perhaps solely, active. All of these studies are under way, the latter temporarily hampered by lack of precise

chemical information and production difficulties." In statements which follow we shall outline briefly the published results of Eagle and his co-workers and interpolate data from the observations of others.

*Effect of Method of Administration on the Efficiency of Sodium Penicillin in Experimental Syphilis.* This aspect of the problem has been thoroughly studied by Eagle, Magnuson and Fleischman.<sup>16c</sup> They used rabbits recently successfully injected intratesticularly (5 to 7 weeks) with the Nichols strain of *T. pallidum* and injected 9 different lots of penicillin varying in purity from 130 to 1025 Oxford u./mg. in accordance with 13 different schedules on which the interval between injections varied from 15 minutes to 4 days, the total number of injections from 4 to 50, and the duration of treatment from 3 hours to 16 days. In each of the schedules, 3 to 9 rabbits were treated at each of 3 to 7 dosage levels, which usually varied in 2-fold steps. Since no clear-cut differences were noted in the lots of drugs studied, the various brands of penicillin were not compared. Cure was determined by immediate observations on the disappearance of spirochetes and by lymph node transfers at proper intervals. The results of these experiments indicated that the curative dose of sodium penicillin in rabbits was affected to a striking degree by the number of injections. The greater that number, the less was the total quantity of penicillin required for cure. On the other hand, they noted that, provided only that the interval between injections was sufficiently great to avoid cumulative effects on the blood penicillin level (in which case therapeutic efficiency was paradoxically diminished), it made no difference whether penicillin was administered every 4 hours, twice daily or daily; an equal number of injections at a given dosage level produced equivalent effects. The relationship of blood levels and the therapeutic results of penicillin are under study; although the therapeutic action of penicillin clearly involves both the tissue concentrations and the time over which

\* These same authors<sup>2a</sup> observed similar results in early latent syphilis (8 months' durations in rabbits).

they act, the latter time factor is by far the more important. Low concentrations acting over a long period of time (*i. e.*, many small injections) were more effective than high concentrations acting over a short period (namely, a few large injections to the same total dose). Within the time limits of their experiments, the interval between injections was immaterial, provided they were not given too often: for an equal number of injections, treatments once daily were as effective as injections every 4 hours, with a suggestion of an optimum interval of 8 to 12 hours.

On the basis of the present experimental data, Eagle and his colleagues believe that it may be anticipated that the results in the treatment of human early syphilis with sodium penicillin could be significantly improved by (a) prolonging the duration of treatment, (b) increasing the frequency and number of injections, and (c) increasing the total dosage of penicillin. The use of a suspension of calcium penicillin in oil and beeswax, or the administration of penicillin in a continuous intravenous, intramuscular or subcutaneous drip, or any other procedure which delays the absorption and excretion of penicillin would have the same effect as increasing the frequency and number of injections.

They feel that there is reason to believe that the treatment of syphilis with sodium penicillin need not be carried out in hospitalized patients, but that it may be given on an ambulatory basis once or twice daily without necessarily sacrificing therapeutic efficacy, provided only that the patient receives the requisite total number of injections. The use of calcium penicillin in oil and beeswax, or of similar devices to delay the absorption and excretion of penicillin, may permit treatment to be given as infrequently as twice weekly, and perhaps even irregularly within that time interval.

The total curative dose ( $CD_{50}$ ) of penicillin on the best schedule here tested with 500 u./kg. or approximately 0.3 mg./kg. of penicillin G. Milligram for milligram, penicillin is therefore 10 to 20 times as

effective as mapharsen in the treatment of rabbit syphilis. In the human infection, however, penicillin is apparently only 2 to 4 times as active as mapharsen, milligram for milligram.

With either penicillin or mapharsen, rabbit syphilis is easier to cure than the human disease, requiring less than one-fourth to one-eighth as much mapharsen, and less than one-twentieth to one-fortieth as much penicillin.

In experiments designed to test the effect on therapeutic efficacy in experimental syphilis of delaying absorption of penicillin as postulated above by Eagle, Magnuson and Fleischman,<sup>16c</sup> this same group<sup>16b</sup> found that their deductions regarding the influence of delaying absorption and thus prolonging blood levels on curative action was correct. Using rabbits treated 5 to 7 weeks after testicular inoculation with 9 different lots of penicillin (4 were commercially prepared suspensions of the calcium salt in peanut-oil and beeswax) it was found that the curative dose ( $CD_{50}$ ) of the oil-beeswax mixture, given daily for 4 days, fell from 39,000 to 8000 to 3500 u./kg. as the percentage of beeswax increased from 0 to 3 to 6% (by volume). The corresponding  $CD_{90}$  values were 80,000, 16,000 and 8000 u./kg. When calcium penicillin in oil and beeswax (4.8 to 5.3% by weight) was administered (a) as a single injection, (b) twice at 8 hour intervals, (c) daily for 4 days, (d) twice daily for 8 days, and (e) twice weekly for 8 weeks, the  $CD_{50}$  dose was, respectively, (a) 50,000, (b) 54,000, (c) 3500, (d) 800 and (e) 1500 u./kg. The corresponding  $CD_{90}$  doses were as follows: (a) 100,000, (b) 90,000, (c) 8000, (d) 1800 and (e) 2000 u./kg. In contrast the  $CD_{50}$  of penicillin in aqueous solution given (a) as a single massive injection, (c) daily for 4 days, and (d) twice daily for 8 days was (a) greater than 600,000, (c) 50,000, and (d) 1770 u./kg. respectively (that is, 2 to 12 times the curative dose of the oil-beeswax preparation similarly administered). The curative dose of penicillin, aqueous solution or oily suspension, varied

with the number of injections into which the treatment was divided. They found that if one compares the efficacy of the 2 preparations on the basis of number of injections rather than the dosage: (a) to cure syphilis in 1 day with a total of 50,000 units required 1 injection of the oil-beeswax preparation, and 12 injections of the aqueous solution; (b) to cure syphilis in 4 days with a total of 3500 u./kg. required 4 injections of the oil-beeswax preparation and 16 of the aqueous solution; (c) to cure syphilis in 8 days with 800 u./kg. required 16 injections of the oily preparation and 32 of the aqueous solution. Thus the total dose of aqueous solution had to be divided into 2 to 14 times as many injections as the oil-beeswax suspension in order to be equally effective. This superiority of the oil-beeswax suspension was especially striking in schedules involving relatively large injections. The smaller the individual dose of penicillin, the less pronounced was the margin of superiority. Kolmer and Rule<sup>26a</sup> also studied the therapeutic activity of penicillin in single and multiple doses in isotonic solution of sodium chloride and peanut oil-beeswax by intramuscular injection. They found that in the treatment of acute syphilitic orchitis of rabbits the minimal single curative dose of commercial and purified amorphous sodium salts of penicillin in isotonic solution of sodium chloride by intramuscular injection was more than 160,000 u./kg. of weight. For penicillin suspended in peanut oil-beeswax, the corresponding dose was 10,000 units. When given once a day for 8 days in succession, the minimum curative dose of the salt solution of penicillin was approximately 5000 u./kg. per dose, totalling 40,000 units. When given intramuscularly twice daily for 8 days in succession, it was approximately 1000 u./kg. per dose, totalling 16,000 units. The corresponding doses for penicillin suspended in sterile peanut oil and beeswax by intramuscular injection approximately 1000 u./kg. per dose, totalling 8000 units and less than 1000 u./kg. per dose or less

than a total of 16,000 units. In confirmation of the results of others, they noted that penicillin suspended in peanut oil-beeswax by intramuscular injection, therefore, was found to be therapeutically more effective in the treatment of acute syphilitic orchitis of rabbits than that administered dissolved in isotonic solution of sodium chloride by intramuscular injection. The commercial penicillin employed in these experiments contained approximately 88% penicillin G and the purified approximately 92% G. Both commercial and purified lots gave essentially similar results. The above results are, in addition, a large scale elaboration of the concept described in a preliminary way with few rabbits by Raiziss in 1944<sup>45</sup> "that penicillin in oil suspension is therapeutically somewhat more active in experimental rabbit syphilis than penicillin in aqueous solution. The superiority of the oil suspension, however, lies chiefly in the fact that the administration of the drug can be reduced to one treatment a day."

*The Effect of the Various Penicillins and Impurities in Experimental Rabbit Syphilis.* Not only does dosage, method of administration, etc., play a rôle in the effect of the drug on *Spir. pallida*, but, as was indicated in the *in vitro* studies, the type of penicillin and impurities also are factors conditioning the *in vivo* action on this organism. Continuing their study of the relative activity of partially purified penicillin and of crystalline penicillin G on *T. pallidum*, Dunham and Rake<sup>13</sup> showed in experimental rabbit syphilis that partially purified penicillin, 330 u./kg. —protected (not cured) a large proportion of rabbits from local and generalized infection when 66,000 u./kg. of body weight were administered intramuscularly in the leg 5 hours after a suspension of spirochetes had been rubbed into an incision on the back; the same dose of crystalline penicillin G in another experiment failed to protect. That penicillin G, however, has spirocheticidal action *in vivo* is evidenced by the fact that 166,000 u./kg. of this preparation prevented the develop-



ment of local syphilitic lesions on a large proportion of the rabbits. On the other hand, an alumina adsorbate of partially purified penicillin showed a greater activity *in vivo* than did crystalline penicillin G. Thus, again, it is suggested that some impurities in the crude penicillin product have antitreponemal power. As stated above, Eagle and Musselman<sup>17c</sup> found a varying therapeutic activity against a cultured strain of *Spir. pallida* (Reiter) in crystalline samples of penicillin F, G, K and X. Subsequently they studied this problem in experimental rabbit syphilis. Their observations indicated differences in the relative activity of the several penicillins *in vivo* far exceeding those observed *in vitro*. The curative dose (CD<sub>50</sub>) of commercial penicillins, which probably consisted largely of penicillin G, had been found by Eagle, Magnuson and Fleischman (cited by Eagle and Musselman<sup>17c</sup>) to be 1650 u./kg. when given every 4 hours for 20 injections. However, with penicillin K similarly administered, preliminary data indicated that even 16,000 u./kg. were not curative. In an attempt to assess the cause of this discrepancy Eagle and Musselman<sup>17c</sup> also noted that in the treatment of experimental syphilis, penicillin K has been far less efficient than other penicillin compounds. This low therapeutic activity of penicillin K has been found by them to be due to the fact that penicillin K disappears from the blood more rapidly than do the other penicillins. One hour after the injection into rabbits or man of penicillin G, F, X and K, blood levels of K were one-fourth to one-eleventh of those observed with the other penicillins, and K persisted at demonstrable levels for relatively shorter periods. The recovery of penicillin K in the urine averaged 30 to 35%, compared with an average recovery from G, F and X of 74% in rabbits and 91% in man.

These data suggest that penicillin K is inactivated in the body to a greater extent and more rapidly than penicillins G, F and X and indicate that the amount of

K in commercial penicillin should be kept minimal.\*

It is of interest to note that clinically, penicillin G is the preparation which seems to have the greatest effect on *T. pallidum* as demonstrated by accelerated disappearance of surface organisms from darkfield positive lesions. For example, Olansky and Putnam<sup>43</sup> found that penicillin G appeared equally effective as compared with several commercial penicillin preparations and penicillin X appears less effective than penicillin G in causing the disappearance of spirochetes from darkfield positive lesions. In a more extensive study, Tucker and Robinson<sup>55</sup> noted that penicillin G, given to 35 patients with early syphilis in amounts ranging from 0.038 to 87 mg./kg., yielded an inverse relationship between dosage of this penicillin type and the time required for disappearance of treponemes. While, as has frequently been demonstrated, disappearance of surface organisms from syphilitic lesions is a false criterion of curative action, this property of a preparation in competent hands is a useful rapid indicator of possible differences in various preparations.

*Relation of the Size of the Inoculum and the Age of the Infection to the Curative Dose of Penicillin in Experimental Syphilis.* Eagle, Magnuson and Fleischman<sup>16c</sup> have reported an extensive investigation in this problem which is important from the standpoint of chemical prophylaxis of syphilis. As previously stated, Eagle and Musselman<sup>17b</sup> showed that when penicillin is added to a suspension of the Reiter strain of *Spir. pallida* the number of viable organisms falls off at a rate which is largely independent of the number of organisms, and which varies with the concentration of penicillin in the range of 0.01 to 1 u./cc. If the initial number of organisms is increased, a larger proportion must be killed in order to prevent growth in subculture. Thus penicillin must be allowed to act for a longer period of time, or, the time factor remaining constant, the concentration of penicillin must be increased within the range which

\* See also, Turner, Cumberland, and Li, *Am. J. Syph., Gonorr. and Ven. Dis.*, **31**, 476, 1947.

affects the rate of its spirocheticidal action. These *in vitro* relationships were believed to apply to *in vivo* situations. Eagle and his co-workers showed in the present study that precisely these relationships have been found to obtain in experimental syphilis. If rabbits are inoculated with varying numbers of organisms, there is a corresponding variation in the amount of penicillin necessary to abort the infection, when administered 4 days after inoculation. Conversely if the size of the inoculum is fixed and if the animals are treated at varying intervals after their inoculation, there is a progressive increase in the amount of penicillin necessary to abort the infection, because of the *interim* multiplication of spirochetes *in vivo*. If there is a small inoculum and treatment during the incubation period, extraordinarily small doses of penicillin are sufficient to abort experimental infection of rabbits with syphilis. There is also suggestive evidence that these observations may be applicable to the problem of aborting human infections with syphilis.

*Combining Chemotherapy With Penicillin, Arsenicals and Bismuth Compounds.* In the pre-penicillin era, while use of one antisiphilitic agent alone was effective against syphilis, combined chemotherapy (arsenical and heavy metal) consistently seemed to give an ultimate advantage to the patient. Although penicillin alone in adequate dosages seems effective in early syphilis, the failure rates are approaching, if not exceeding those obtained prior to the advent of penicillin, albeit with lessened toxicity. In view of the demonstrated efficacy of combined therapy (arsenical and heavy metal) the penicillin investigating triumvirate of Eagle, Magnuson and Fleischman<sup>16</sup> set out to see whether there was a synergistic action of penicillin and mapharsen (oxophenarsine hydrochloride) in the treatment of experimental syphilis such as had been previously demonstrated by Eagle<sup>15a</sup> for metal chemotherapy. In this earlier study it was shown that moderate doses of bismuth and mapharsen used in conjunction are

far more effective than even large doses of an arsenoxide used alone. In the present study Eagle and his colleagues identified a qualitatively similar and quantitatively even more pronounced additive effect when penicillin was supplemented by mapharsen. In the therapy of experimental rabbit syphilis small fractions of the curative doses of penicillin and of mapharsen were curative when used in conjunction. The two drugs together were so much more effective than either alone as to suggest more than a single additive effect was involved. Regardless of the implications of the already clearly demonstrated fact that, clinically, arsenical and penicillin used concurrently are an effective combination, the increased incidence of severe reactions is a limiting consideration of no small moment (Stokes, Beerman and Ingraham<sup>52</sup>).

The effectiveness of combining bismuth with penicillin in the treatment of syphilis has had little attention in the literature to this time. Kohmer and Rule,<sup>26b</sup> under the conditions of their study, showed that not only oxophenarsine hydrochloride by intravenous and intramuscular injection but bismuth and potassium tartrate in oil by intramuscular injection has decided synergistic or additive therapeutic effects in the treatment of acute syphilitic orchitis of rabbits with penicillin.

*Fever.* In their study on the effect of hyperpyrexia on the therapeutic efficacy of penicillin in experimental rabbit syphilis, Eagle, Magnuson and Fleischman<sup>16a</sup> set out to determine *in vivo* whether fever has a similar favorable effect in the therapeutic efficacy of penicillin which Eagle and Musselman<sup>17b</sup> had shown was the case *in vivo* and others had shown with the arsenicals.<sup>39a</sup> In general this study confirms *in vivo* the previously cited *in vitro* results that the rate at which the Reiter strain of cultured *Spir. pallida* are killed by penicillin, increases with temperature throughout the range of 8° to 40° C. (see above). When penicillin was injected intramuscularly in syphilitic rabbits every 2 hours for 16 injections, it required

30,000 and 60,000 u./kg. to cure 50 % and 90 % of the animals respectively. When the body temperature, during the administration of penicillin, was raised by approximately 3° to 4° F. over an average 10 hour period, the total curative dose fell to 8000 (CD<sub>50</sub>) and 3000 (CD<sub>90</sub>) u./kg. The 8- to 10-fold increase in the therapeutic efficacy of penicillin indicated by those figures is a minimum, since in the fever experiment, 75 % of the total amount of the penicillin administered was concentrated in the 6 injections given over the 10 hour fever session. This asymmetric distribution would tend to diminish the overall efficacy of penicillin as such. The favorable effect of fever on the therapeutic activity of penicillin tends to reflect the enhanced spirocheticidal effect of penicillin at higher levels of temperature. In addition, fever may have a spirocheticidal action if its own, additive or synergistic.\*

**Penicillin Resistance.** Using the criterion of treatment resistance which we have employed,<sup>4</sup> (failure of lesions to heal and persistence of organisms in lesions in spite of treatment), and not mere irreversibility of positive serologic reactions, it is evident that practically no clinical penicillin resistance has been observed. The only reported cases (there are certainly others, unreported) were by Moore<sup>39</sup> and Tyson.<sup>57</sup> Moore's patient† had a cutaneous gumma which failed to respond to 4,800,000 units of penicillin but did heal promptly after several weeks of arsenical and bismuth therapy. Tyson's patient with early syphilis received 2,400,000 units of penicillin over a period of 5 days. The chancre did not heal, although the serologic reactions had become negative after several weeks. The reactions subsequently became positive and secondary lesions appeared. Combination of fever with an additional 600,000 units of penicillin gave an excellent response. In view of the uncertainties of the correct time-dosage relationship of penicillin, it is likely that while

this represents clinical treatment resistance, the dosage (and quality of the drug used) may have been inadequate to control the progression rather than the development of an actual penicillin resistant strain of *Spir. pallida* induced by inadequate dosage or other factors presumed to induce this phenomenon.

In passing, but not entirely germane to the present topic, penicillin has been shown clinically to be effective in patients with manifestations of syphilis resistant to arsenical and heavy metal therapy (Noojin and co-workers,<sup>42</sup> and Nelson and co-workers<sup>41</sup>).

The first experimental evidence that spirochetes might develop penicillin-resistance was the study of Dunham, Hamre, McKee and Rake<sup>12</sup> who showed that inadequate therapy of syphilis in the rabbit resulted in the production of a more resistant strain of *T. pallidum*. This study emphasizes the importance of adequate initial therapy and raises the question of the effect of inadequate penicillin treatment for syphilis given to patients with gonorrhea who might also be in the incubation period of syphilis, on *T. pallidum*. Bessemans and Derom,<sup>56</sup> in their second note, reported studies on the influence of subtherapeutic doses of penicillin administered during the incubation period of experimental rabbit syphilis. They observed that the incubation of syphilis in these subtherapeutic doses of penicillin did not abort the infection or render it asymptomatic (Eagle *et al.*<sup>35</sup>), but retarded the appearance of clinical manifestations. This again is no evidence in the direction of demonstrating a penicillin resistance, but perhaps is merely an expression of the spirochetistatic action of inadequate penicillin dosage. Tung and Frazier<sup>58</sup> did not note the development of increased resistance or tolerance to penicillin in cultures of the Reiter strain of *T. pallidum* after being subjected to 15 passages through media containing the preparation. Kolmer and Rule<sup>59</sup> have produced experi-

\* Craig, Schwemlein and Kendall: J. Lab. and Clin. Med., 30, 1016, 1945.

† Reported by Hahn: Am. J. Syph. Gonorr. and Ven. Dis., 31, 542, 1947.

mental evidence against the existence of acquired penicillin resistance. They found that a minimal curative dose for acute testicular syphilis of rabbits (Nichols-Hough strain) of commercial penicillin in aqueous solution by intramuscular injection 3 times a day for 10 successive doses was apparently slightly more than 1000 u./kg. (10,000 units total) and probably a little less than 5000 units per dose (total dose: 50,000 units). This strain did not show any evidence of acquired resistance or tolerance to penicillin after 3 consecutive passages through the testicles of rabbits when they were treated with subcurative amounts of the compound. While the last word has not been said on the problem of penicillin resistant *Spir. pallida*, the lack of evidence from the clinical standpoint of real treatment resistance among so many patients with early syphilis undoubtedly treated unwittingly with an inadequate dosage, speaks eloquently against the possibility of such a phenomenon. The situation is well summarized by Tainter,<sup>54</sup> who stated that "there is as yet no absolute evidence that the development of penicillin resistant strains has occurred in clinical practice in any disease."

**THE MODE OF ACTION OF PENICILLIN AGAINST *T. PALLIDUM*.** Practically nothing of a definitive nature is known about the actual site of action or mechanism of action of penicillin on *T. pallidum*. The vast amount of experimental data already accumulated has seemed largely to define as precisely as possible the condition under which this new method of treatment works to the best advantage of eliminating infection with syphilis. In this connection Eagle, Magnuson and Fleischman<sup>16c</sup> have summarized our present knowledge so concisely that it is quoted *verbatim*.

*"Mode of Action of Penicillin.* The mode of action of penicillin differs from that of the arsenicals in several fundamental respects. When a trivalent arsenical such as mapharsen is injected, it is bound by the organisms in competition

with the tissues. The combination is largely completed within a short time, and the spirochetes subsequently die or survive in relation to the amount so bound and their varying individual susceptibility. A single exposure to a temporarily high concentration of the arsenical apparently kills as many organisms as repeated exposures to small concentrations. It has been shown in both animals and man that the curative dose of mapharsen in syphilis is essentially the same whether the drug is administered in a single massive injection, in 10 to 20 large injections administered over a period of days, or in many small injections administered over a period of months. With penicillin, on the other hand, therapeutic efficacy was enormously enhanced merely by subdividing treatment into a large number of injections. The essential difference seems to be the fact that penicillin is not demonstrably bound and concentrated by the organisms, so that its action depends on the length of time for which effectively spirocheticidal levels are maintained in the body fluids. It is this introduction of the time factor, the necessity for maintaining an effective level, which primarily distinguishes the kinetics of the spirocheticidal action of penicillin from that of, *e. g.*, mapharsen.

"The therapeutic efficacy of penicillin, therefore, rests primarily on 2 factors: its concentration in the body fluids, and the period of time for which the organisms are exposed. Both factors contribute to therapeutic efficacy; but it is the clear implication of the experimental data here reported that of these 2 variables, the time factor is by far the more important."

A good summary of much of our present knowledge of the action of penicillin, especially on *T. pallidum*, has been prepared by Frazier and Frieden.<sup>22</sup> Since this compilation little has been added except to clarify certain minor points. Although the precise manner in which penicillin acts to destroy microorganisms is unknown, it is generally assumed that it interferes with the normal completion of some meta-

bolic transformation, thus inhibiting the development of the cell and leading to its eventual death. While it has been shown that penicillin undoubtedly has a direct spirocheticidal action *in vitro*, the reasoning with regard to the mechanism of this action follows somewhat along the lines proposed to explain that of the arsenicals. Because of this similarity, a brief statement of the mechanism of the antispirochetal action of the arsenical compounds is in order. It was thought for a long time that the arsphenamines did not have a direct action on spirochetes but became effective only when changed in the body to some active (avid form). This was postulated to be an arsenoxide. Eagle,<sup>15b,c</sup> however, initiated a critical series of *in vitro* studies which demonstrated that not only do the arsenicals have a direct antispirochetal action in concentrations effective only *in vitro*, but that tissue extractions (testicular) inhibited rather than enhanced this activity. Eagle then tested the hypothesis of Voegtlin, Dyer and Leonard<sup>59</sup> that arsenic may combine with the sulphhydryl groups in the organism in the process of its destruction, and he found that various sulphhydryl compounds almost completely abolished the spirocheticidal action of arsenicals and the heavy metals (mercury and bismuth). He believed that the rapid inactivation of the arsenical preparations by sulphhydryl compounds indicated that the drugs owe their therapeutic activity to similar combinations with sulphhydryl groups in the spirochetes. Penicillin too can be inactivated by various sulphhydryl compounds. This has led Cavallito and Bailey<sup>9</sup> to believe that the main mode of action of many antibiotic substances rests in their facility to interfere with normal function of sulphhydryl groups in bacterial metabolism. Chow and McKee<sup>10</sup> concluded that inactivation of penicillin by cysteine (a sulphhydryl compound) may involve both the sulphhydryl and the amino groups of the cysteine molecule. Leonard<sup>23</sup> suggested that "until it can be proven that penicillin binds to the SH groups of

reduced bacterial protein in proportion to the number of SH groups in such protein . . . the actual point of attack of penicillin on microorganisms cannot definitely be concluded to be upon thiols of the organism." Cavallito,<sup>8</sup> on the other hand, disagrees with Leonard that penicillin needs to bind protein-SH in direct proportion to the number of SH groups in protein. Frazier and Frieden<sup>22</sup> summarize this problem as follows: "The similarity of the effects of sulphhydryl compounds on penicillin and the arsenicals may be indicative of a possible similarity in the modes of action of the 2 types of antispirochetal agents. It is important to note, however, that significant differences exist with respect to such effects. While the inactivation of penicillin by cysteine proceeds slowly, the addition of this substance to suspensions of *T. pallidum* exposed to the action, for example, of arsphenamine, results in the immediate inhibition of the antispirochetal action. The fact that the arsenicals can be regarded as general protoplasmic poisons, while penicillin is not, may also be an indication of the essentially dissimilar nature of their respective modes of action."

The effects of penicillin on the morphology of various organisms have been reported repeatedly since the introduction of this type of chemotherapy.<sup>7,11,19,20,23,38,60</sup> Visible changes on the bacterial cell, inhibition of cell division, elongation and hypertrophy of the cell as well as changes in the actual shape of the bacterial cell have been observed by direct microscopic observation or by the study of electron microscopic pictures.

Since *T. pallidum* is a motile organism, direct darkfield and electron microscopic observation of the effects of penicillin on its morphology and motility promised to yield information of value in determining the sort and mode of antispirochetal activity. While a number of interesting observations have been made by Eagle, Dunham and Rake, and Frazier and his colleagues, their significance is not clear. Early in their work Eagle and his asso-

ciates, as previously noted, observed that *Spir. pallida* under the influence of doses of penicillin adequate to render the organisms non-viable remained actively motile for a period of 8 to 24 hours. Dunham and Rake observed in their *in vitro* studies that in cases where immobilization was incomplete, there was only sluggish motion. The last form of motion to be lost was bending of the body of the spirochete near the midpoint. They believed that it may well be that axial rotation is caused by the flagella revealed by the electron microscope, and that these are more sensitive to the action of impure penicillin than are the bodies of the organisms. The decrease in motility on exposure to partially purified penicillin suggested the possibility that these spirochetes might no longer be infectious. Even in the case where 90% of the spirochetes in the mixture used as inocula were immotile, there should have been more organisms than were necessary to cause infection if they had not been altered by exposure to the drug. As previously stated, spirochetes exposed to 1100 u./ml. of the partially purified preparation of penicillin are non-infectious for rabbits when injected intratesticularly, although many of them are still motile at the time of injection. Frazier and Frieden report that changes in the length of spirochetes were first observed in their laboratory by H. G. Sleeper. The relative distribution of long and short forms of the spirochete in material from early lesions observed in the darkfield, varied in such a way as to suggest that the changes observed were related to the effect of penicillin. Within 90 minutes after the first injection of 20,000 units of this drug, there was a relative increase in the number of the long forms of the spirochete. This increase was progressive until no more organisms could be found in the darkfield. This relative increase in long forms even occurred in a case when no such forms were seen before treatment. Frazier and Frieden<sup>22</sup> wonder whether this phenomenon of elongation of spirochetes may not

be an indication of excessive growth and delayed cell division. Tung and Frazier<sup>56</sup> also made observations on penicillin sensitivity and morphology of the Reiter strain, of *T. pallidum* after cultivation in media containing penicillin. Electron micrographs of spirochetes grown in normal and penicillin-containing media were made with an RCA model electron microscope. They found that "While some of the spirochetes growing for the first time in media containing a sublethal concentration of penicillin became somewhat elongated, a tremendous increase in the length of individual organisms was observed in subcultures exposed to the same amount of penicillin, namely, from 0.05 to 0.1 u./ml. Under normal circumstances, the average length of the Reiter strain of spirochete is about 20  $\mu$ . Occasionally, organisms of 40  $\mu$  were seen in cultures exposed for the second time to penicillin, long forms of from 100 to 150  $\mu$  could easily be found in each oil immersion field. Most of the organisms were of the order of from 40 to 60  $\mu$  in length, but occasionally giant forms which had grown beyond the limits of the microscopic field were seen. . . . No statistical measurement was carried out, since no attempt was made to break up the large masses of tangled and matted forms composing the culture. The long forms had no appreciable increase in width. They appeared to be single organisms with stretched-out spirals and sluggish motility." The electron micrographs confirmed the impression that the long forms were single organisms. It is of interest to note that while the short spirochetes grown in normal media possessed flagella, none of the long forms were flagellated. Only an occasional, comparatively short spirochete in the midst of the long ones was found to have flagella.

"The life of the long forms were short. The elongated organisms appeared in the culture after 24 hours of incubation and gradually disappeared after 72 hours. A few moderately long spirochetes, measuring around 60  $\mu$ , were observed when the

organisms were transferred back to normal media after several passages through media containing penicillin.

"Although a few long forms were seen in cultures exposed for the first time to a sublethal concentration of penicillin, many more long forms began to appear after from 42 to 72 hours of incubation in cultures exposed to an inhibitory amount of the antibiotic agent (0.125 u./ml.). Most of the inoculated organisms survived a concentration of 0.125 u./ml. of penicillin and became elongated as the penicillin was vanishing from the culture

medium. These long forms could be seen in the culture for about 4 days.

"In view of the possibility that commercial penicillin and crystalline penicillin might act differently on the spirochetes, as was shown with a pathogenic strain of *T. pallidum*, the experiment was repeated with penicillin sodium G having a potency of 1650 u./mg. It was found that both the pure and partially purified penicillin possessed the same potency of action and produced the same effect on cellular growth."

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## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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## PATIENT'S PLIGHT, DOCTOR'S DESPAIR—THE COMMON COLD

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OFTEN ignored because of the widespread belief that nothing much can be done about the common cold ("there is only one way to treat it—with contempt" is a practice as current today as it was in ancient Rome), the most democratic of ailments afflicts the average American from 1 to 4 times a year and represents an annual collective economic loss of \$1,000,000,000. While the common cold rarely is a direct cause of death, it precedes or incites such serious infections as bacterial pneumonias, subacute bacterial endocarditis, septicemia and meningitis, and frequently precipitates the symptoms of coronary occlusion, peptic ulcer and other diverse diseases.<sup>9</sup>

Although it has never furnished the theme for a Hollywood motion picture or a year's run in the Broadway theatre, the common cold masks a human interest document that is neither prosaic nor lacking in drama. Infections of the respiratory tract, for example, cause more loss of time from industry and from schools than all other diseases combined.<sup>6</sup> Indeed, industry has lost 20 times as much time by the common cold as by accidents.<sup>11</sup> As has been said of the weather, so has been said of the common cold: "Everybody talks about colds but nobody does anything about them." The facts of the matter are: more has been done about the weather than about colds.

There are 2 purposes to this review: (1) to discuss briefly common cold knowledge; and (2) to propose a plan for mobilizing against the patient's plight. There are

things the medical and allied professions can do beside despair.

**COMMON COLD BACKGROUND.** It is generally held that the common cold is caused by a filtrable virus which is responsible for most colds occurring in epidemic form. Small outbreaks of colds, however, are sometimes caused by microorganisms capable of invading the healthy mucous membrane in the absence of a concurrent virus infection. In this country there are 3 main peaks of incidence each year: one occurs in October and November, a second early in January, and the third in March and April. The degree of susceptibility and resistance varies from one individual to another and from year to year. A certain degree of immunity develops as a result of a cold but it is of short duration, not more than several weeks or months after an attack.

Local resistance appears to be largely dependent on an intact mucous membrane, upon mucociliary activity, and presumably upon lysozyme.<sup>2a</sup> Local resistance may be impaired by structural abnormalities, such as nasal polypi, hypertrophied adenoid tissue, or chronic sinusitis where pathogenic bacteria are harbored and normal drainage is impaired. Although the precise rôle remains unclear, there is evidence that chilling the surface of the body causes a reflex vasoconstriction and a fall of temperature of the mucous membrane favoring the invasion of viruses.<sup>7</sup> Observations by Paul and Freese<sup>8</sup> suggest that sudden chilling of the body may bring on an attack in a person who has had a recent infection or a recent contact, but

only if such a condition accompanied the chilling.

It is generally assumed by most students of the common cold problem that abnormal vasomotor disturbances in the nasopharynx not only cause local injury to the tissue and facilitate infection by the pathogenic agents which are present, but that similar reactions may be caused by various irritants or by allergens in the air or food, or by injection. Furthermore, the vascular tone of the upper respiratory tract may be disturbed by systemic derangements and physiologic imbalances in the vegetative nervous system. Hence, such factors as constitution, fatigue and emotional strain are of etiologic importance in the common cold. In the few studies available, the histologic changes of the nasal mucous membrane in the common cold are almost identical with those of influenza in animals and in man.

It is reasonable to conclude that the common cold is not a definite single disease, but comprises a group of different affections.

**COMMON COLD THERAPY.** Although methods for the prevention of colds have been directed along various lines, it can be stated unequivocally that none of the procedures is effective.

From time to time claims are advanced advocating a special diet either for the prevention or the cure of colds. The dietary measures most frequently recommended for the prevention of colds include a high protein diet, a diet low in carbohydrates, and large quantities of citrus foods, presumably to establish "alkalinization." None of these theories is supported by carefully controlled studies. Deficiency states may predispose to certain infections, but the supplying of extra vitamins and other food elements to the individual who shows no signs of deficiency disease does not protect him against colds. So widespread is the belief of the American public that the use of sodium bicarbonate or other alleged antacids is a preventive in the treatment of the common cold that it may really be called a part of American

folklore. Diehl<sup>14</sup> has demonstrated conclusively that the results obtained by "alkalinization" are of little or no value.

A number of procedures have been recommended periodically which have as their objective the conditioning of the body to sudden changes in external temperature of the skin, such as cold shower baths every morning and exercise outdoors followed by hot and cold shower baths. Controlled experiments have been carried out by Gafafer<sup>3</sup> who was unable to show any lower incidence of colds in people who followed these practices when compared with a group who did not.

In attempting to reduce the number of colds in susceptible persons, vaccines containing a wide variety of microorganisms commonly found in the respiratory tract have been employed. Extensive studies by Diehl and others<sup>16</sup> have demonstrated that cold vaccines, whether given parenterally or by nasal spray, do not prevent colds. As for cold vaccines given orally, the *Journal of the American Medical Association* has this to say editorially:<sup>5</sup> "Recent communications to the offices of the American Medical Association indicate that the prescription and sale of cold vaccines is again taking place on a large scale. This, in the face of the recognized lack of scientific evidence for the value of these preparations, is indication of irresponsibility on the part of some manufacturers of pharmaceuticals. The scientific evidence against the value of oral cold vaccines is overwhelming; consequently individual physicians and firms who deal in pharmaceuticals and who lend themselves to the wholesale uncontrolled distribution of such preparations are perpetrating an unwarranted commercial assault on the public pocketbook."

The employment of ultraviolet light or germicidal aerosols for sterilizing the air of rooms where crowding is prevalent is believed by some to offer a means for reducing the incidence of colds. Recent United States Public Health Service studies,<sup>10</sup> however, cast serious doubt on the hope that colds and other respiratory ail-

ments can be banished by the chemical treatment of air with glycol aerosols and irradiation with ultraviolet light.

The treatment of the common cold consists mainly in the relief of symptoms as they arise. Treatment should never be standardized but should be suited to the needs of each patient. During the earliest stages of the common cold the prime objective is to supply moisture by means of steam inhalations to the stricken upper respiratory passages. Alcohol has been utilized for generations to abort impending colds or to treat them. In reasonable doses it causes peripheral vasodilatation and reestablishes circulation in chilled cutaneous and mucosal surfaces. Rest in bed, especially if fever is present, diminishes the severity of the common cold, limits its spread to others, and reduces the frequency of complications. It has stood the rigid test of time as a most sane and effective measure.<sup>2b</sup>

Little attention need be paid to fluids in the average uncomplicated cold. It is probably best to let thirst to a great extent determine the fluid intake. Cathartics, long employed as a home remedy for colds, have no value; their excessive use may lead to dehydration. Although salicylates and other fever-reducing medicaments have no effect on the infectious process, they do control headache and muscular aches. These should not be given routinely but only if necessary. Sulfonamide compounds and penicillin are ineffective in virus-initiated colds. Their employment in an uncomplicated case of the common cold may give rise to strains of drug-fast pathogenic bacteria resistant to treatment with either.

Even temporary relief from the discomfort of nasal obstruction justifies the use of proper nasal medication.<sup>4</sup> Nasal vasoconstrictors can satisfactorily relieve nasal congestion for varying periods of time and when judiciously employed often aid in promoting adequate drainage from the nasal sinuses. Liquid nasal medicaments which function on a rational, physiologic basis are compatible with ciliary activity,

do not vary greatly in their pH (5.5 to 6.5) from that of normal nasal secretions, are isotonic, and are non-injurious and non-toxic. The continual use of nasal preparations containing mineral oil sometimes leads to the development of lipoid pneumonia.<sup>2a</sup>

**THE NEED FOR MOBILIZED RESEARCH.** Although organized science has succeeded in the solution of atomic energy, it has not solved the riddle of the common cold. The discovery of atomic energy was made possible because men who knew most about their specialties convened and pooled their knowledge. Whereas in the past fundamental discoveries have been made by isolated workers devoting their leisure time to research, present-day experience indicates that most progress comes from the coöperative effort of individuals having different training and background. Had individual specialists worked on the atomic energy problem piecemeal, it is a question whether the nation could have succeeded in its solution.

In the opinion of Fabricant,<sup>2c</sup> the common cold age-long mystery could be eradicated if the same sort of mobilized research that went into unlocking the atomic age were directed at the cause and cure of colds. If the experience of the past has any meaning, it signifies that colds cannot be eliminated by the efforts of single groups of scientists working in isolation. The common cold contains too many diverse factors for any one individual or group of individuals to solve. Much medical investigation of the common cold in the past has been characterized by inefficiency and *laissez-faire*. Most research men, if the truth be stated bluntly, have been wasting precious time, effort and money by pursuing their individualistic bents in isolated laboratories, clinics and hospitals. A perusal of the vast medical literature on the common cold speaks eloquently in support of such a contention.

The mere accumulation of facts is not enough. It is important to use them to establish new principles or to confirm old

ones. Scientists are well aware that not all discoveries are made to order and that some come off quite by accident. However, the chances of finding a means of curing colds are infinitely better under mobilized research than under the present system. Although lack of funds is one of the major factors in limiting mobilized research, a comprehensive plan by which the common cold may be attacked is just as essential as ample financial support. If the methods of several great industrial laboratories are adopted—and these have provided a number of fundamental discoveries—money invested in fostering unified research will be spent efficiently; there would be time for long-range study and money for apparatus and technical assistance. Instead of hit-or-miss investigation like much common cold research, there would be long-term concentration on the most promising clues.

Recent attempts to find a cure for the common cold have been proving difficult for the Common Cold Research Unit of the National Institute for Medical Research in England. While it has been claimed by spokesmen for this group that promising results are being obtained, a warning has been issued against any optimistic notion that a cure for colds could be discovered without much more research.

In the United States a sanely conceived program to investigate the common cold, according to Fabricant, should function either under Federal or private sponsorship or both. Since there is always the danger that the interests of research work-

ers from a single specialty (epidemiologists, for example) may become narrow, a national convention of various interested investigators should be called to meet under one roof for the purpose of creating a unified research program. Those in attendance should come not only from the medical ranks, but from the allied worlds of chemistry, biology, pharmacology, physiology, bacteriology, pathology, engineering and architecture. Such a group could function democratically as a coördinated team with a unanimity that is now lacking. In convention, it would be necessary to emphasize principles, to point out to each other past errors of approach, and finally to agree on promising lines of investigation for dissemination to designated research centers throughout the country. Out of such a conference would perhaps come a well-knit program of research which conceivably could telescope decades of individualistic groping into years of coöperative endeavor. Funds for a mobilized research program could be obtained, once the need was widely proclaimed, from private individuals, public subscriptions, foundations and from the Federal government.

The responsibility for initiating a program of mobilized research on the common cold rests primarily with those forward-looking clinicians and basic medical scientists who realize the need for eradicating the common cold scourge.

The time has come for accepting responsibility.

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# BOOK REVIEWS AND NOTICES

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**DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY.** By CHARLES MAZER and S. LEON ISRAEL. 2nd ed. Pp. 570; 133 ills. New York: Paul B. Hoeber, 1946. Price, \$7.50.

This book was first published shortly before Pearl Harbor. That a 2nd edition should be needed so soon after the war is evidence that interest has remained keen in a field far removed from military medicine and surgery.

No small part of this interest has been due to the book itself. The authors' approach to the various problems of menstrual dysfunction is the eminently practical one of dealing with the primary symptoms that bring the patient to her physician. A concise and lucid exposition of the physiologic and pathologic factors underlying each symptom is followed by a rational program of treatment. Such a book has been badly needed in a field where there has been so much misunderstanding, and so much irrational usage of hormone therapy.

In the new edition full account has been taken of contributions that have been made to the subject during the war. These have been added not as mere addenda or new paragraphs but by incorporation in an extensively re-written text. The authors have therefore preserved the integration of material, and clarity of exposition that made the original edition so readable.

The book retains its pleasing format. It can be recommended highly to general practitioners and gynecologists alike.

C. B.

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**MONOCULAR VISION TRAINING.** By MILDRED SMITH EVANS, Orthoptic Technician, Wilmer Institute of the Johns Hopkins Hospital. Pp. 93; 18 ills. Baltimore: Williams & Wilkins, 1946. Price, \$3.00.

This book is essentially a work book for the use of children within a certain age group. In the opinion of the Reviewer the book would be most useful for children about 7, 8 or 9 years of age. It is for the development and improvement of vision in an amblyopic eye where the amblyopia is

monocular in type and is associated with a strabismus. The book has been well planned, the type in the first part is large and bold-faced, that in the latter part becomes smaller. There is a series of 28 lessons so that exercises given in the instructions could be completed in approximately 1 month's time. The author has had long experience, and the book should be useful in its limited field.

W. F.

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**HENRY SEWALL, PHYSIOLOGIST AND PHYSICIAN.** By GERALD B. WEBB and DESMOND POWELL. Pp. 191; 16 ills. London: Oxford Univ. Press. Baltimore: The Johns Hopkins Press, 1946. Price, \$2.75.

This biography of a beloved American physician is a highly successful combination of sympathetic personal record and analysis of professional accomplishment. The authors have given an interesting account of Sewall's youth and education, his early and important, if too little known, studies on physiology and the fundamental aspects of immunology, and his later days as a distinguished authority on tuberculosis. In preparing the book they were in contact with many of Sewall's friends and scientific acquaintances, and as a result the book abounds in interesting personal reminiscences. Sewall was a scholar of first rank, a writer of genius, and an investigator of unusual perception, and always a gifted and delightful companion. His remarkable literary combination of colloquialism and scientific precision is illustrated by scores of pithy extracts from his papers. As the authors point out, his productivity and clarity of thinking were not impaired even in the final months of his long life. All who are interested in medical history should read the chapter on Sewall's investigations of the toxicity of snake venoms to obtain a proper perspective on the development of toxins and antitoxins. The book is to be commended particularly for its emphasis on the influence of Sewall's extraordinary personality in the stimulation of the younger scientific investigators of his day.

F. L.

## NEW BOOKS

*Cineplasty.* By HENRY H. KESSLER, M.D., PH.D. Foreword by ROSS T. MCINTIRE, Vice-Admiral (MC), USN. Pp. 201; 314 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

*Concise Anatomy.* By LINDEN F. EDWARDS, PH.D., Professor of Anatomy, Ohio State Univ. Pp. 548; 324 ills. Phila.: Blakiston, 1947. Price, \$5.50.

*Histopathology of the Ear, Nose and Throat.* By ANDREW A. EGGSTON, B.S., M.D., Director of Laboratories, Manhattan Eye, Ear and Throat Hospital, and DOROTHY WOLFF, A.B., M.A., PH.D., Research Investigator, Endaural Hospital, New York. Pp. 1080; 505 ills.; 28 color plates. Baltimore: Williams & Wilkins, 1947. Price, \$18.00.

*Cancer—Diagnosis, Treatment, and Prognosis.* By LAUREN V. ACKERMAN, M.D., and JUAN A. DEL REGATO, M.D., Pathologist and Radiotherapist to the Ellis Fischel State Cancer Hospital. Pp. 1200; 749 ills., 42 in color. St. Louis: C. V. Mosby, 1947. Price, \$20.00.

*Osteotomy of the Long Bones.* By HENRY MILCH, M.D., Fellow of the American Academy of Orthopedic Surgeons. Pp. 294; 181 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

*Signs and Symptoms, Their Clinical Interpretation.* Edited by CYRIL MITCHELL MACBRYDE, A.B., M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Washington University School of Medicine. Pp. 439; 74 ills.; 6 color plates. Philadelphia: J. B. Lippincott, 1947. Price, \$12.00.

*Forensic Medicine.* By KEITH SIMPSON, M.D. (LOND.), Lecturer in Forensic Medicine to Guy's Hospital, London. Pp. 335; 114 ills. Baltimore and London: Williams & Wilkins, 1947. Price, \$4.50.

*Skin Manifestations of Internal Disorders (Dermadromes).* By KURT WIENER, M.D., Dermatologist, Mount Sinai, Deaconess and Saint Michael's Hospitals, Milwaukee, Wis. Pp. 690; 400 ills.; 6 color plates. St. Louis: C. V. Mosby, 1947. Price, \$12.50.

*Petticoat Surgeon.* By BERTHA VAN HOSEN. Foreword by DR. A. E. HERTZLER. Pp. 324. Chicago: Pellegrini & Cudahy, 1947. Price, \$3.75.

*Characterization of Organic Compounds.* By F. WILD, M.A., PH.D., F.R.I.C., Fellow and Tutor of Downing College, Cambridge. Pp. 306; 11 figs. Cambridge: The University Press. New York: The Macmillan Company, 1947. Price, \$3.75.

A VALUABLE monograph for both research workers and students. After a discussion of the classification of organic compounds and the methods of separating mixtures, the various groups of organic compounds are presented in the 9 subsequent chapters. The author imparts a wealth of up-to-date well-documented information. The preparation of many modern reagents is described, yet old established methods are not neglected. This book also contains a concise discussion of the methods of determining physical constants such as melting point, boiling point, density, refractive index, optical rotation, etc. The work can be recommended unreservedly. M. E.

*A Short Handbook of Practical Anesthetics.* By HOEL PARRY-PRICE, M.R.C.S., L.R.C.P., D.A. (R.C.S.), Royal Berkshire Hospital. Foreword by CECIL P. G. WAKELEY, C.B., Consulting Surgeon to the Royal Navy. Pp. 127; 50 figs. Bristol, England: John Wright & Sons, Ltd., 1946. Price, \$3.00.

THIS is not a text for students of anesthesia, but an interesting account of practical experience in 25 years of civilian and military anesthesia. Written in a lucid manner, the author's experiences are both interesting and comforting. Many practical points can be found in this volume that are useful in the art of anesthesia. R. D.

*A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears.* By OLIVE GATES, M.D., Pathologist, Massachusetts State Tumor Service; and SHIELDS WARREN, M.D., Assistant Professor of Pathology, Harvard Medical School. With a Foreword by GEORGE N. PAPANICOLAOU, M.D., PH.D. Pp. 182; 50 ills. Cambridge: Harvard University Press, 1947. Price, \$4.00.

*Introduction to Medical Psychology.* By L. ERWIN WEXBERG, M.D., Director, Bureau of Mental Hygiene, District of Columbia. Pp. 171. New York: Grune & Stratton, 1947. Price, \$3.50.

AN exceedingly clear, broad account of the psychology that is important for the medical student and practicing physicians. The author reports in an unbiased way the central ideas of Freud, Watson, Cannon, the Gestaltists and others, and creates an unexpected harmony between strange bed-fellows. Chapters of special interest describe the differing values in man's life, the apparatus of knowledge, and the prolonged childhood of man. E. B.

*The Engrammes of Psychiatry.* By J. M. NIELSEN, M.D., F.A.C.P., Associate Clinical Professor of Neurology and Psychiatry, University of Southern California; and GEORGE N. THOMPSON, M.D., formerly Chief of Psychiatric Service, Los Angeles County General Hospital. Pp. 509; 28 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

*Pharmakologie, Als Theoretische Grundlage Einer Rationellen Pharmakotherapie.* By KNUD O. MÖLLER, Professor der Pharmakologie an der Universität Kopenhagen. Pp. 744; 54 figs. Basel, Switzerland: Benno Schwabe & Co., 1947. (Imported by Grune & Stratton.) Price, Fr. 48.

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### NEW EDITIONS

*Diseases of Children.* Edited by DONALD PATERSON, M.D. (EDIN.), F.R.C.P., and ALAN MONCRIEFF, M.D. (LOND.), F.R.C.P. Vol. I. Contributions by 29 Contributors. 4th ed. Pp. 771; 154 ills. Baltimore and London: Williams & Wilkins, 1947. Price, \$9.00.

*Water Supply and Sewerage.* By ERNEST W. STEEL, C.E., Consulting Engineer to Instituto Nacional de Obras Sanitarias, Venezuela; Member American Society of Civil Engineers. 2nd ed. Pp. 666; 264 figs. New York and London: McGraw-Hill, 1947. Price, \$6.00.

*The Development of Modern Medicine.* By RICHARD HARRISON SHRYOCK. 2nd ed. (1st Borzoi ed.) Pp. 472; 10 ills. New York: Knopf, 1947. Price, \$5.00.

*May's Manual of the Diseases of the Eye.* By CHARLES A. PERERA, M.D., Assistant Clinical Professor, College of Physicians and Surgeons, Columbia University. 19th ed. Pp. 521; 387 ills., 93 in color. Baltimore: Williams & Wilkins, 1947. Price, \$4.00.

*A Handbook of Ocular Therapeutics.* By the late SANFORD R. GIFFORD, M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School. Revised by DERRISK VAIL, M.D., D.O. (OXON.), F.A.C.S. 4th ed. Pp. 336; 66 ills. Philadelphia: Lea & Febiger, 1947. Price, \$5.00.

*Textbook of Medicine.* By VARIOUS AUTHORS. Edited by SIR JOHN CONYBEARE, K.B.E., M.C., D.M. (OXON.), F.R.C.P., Physician to Guy's Hospital. 8th ed. Pp. 1170; 56 ills. Baltimore and London: Williams & Wilkins, 1946. Price, \$8.00.

This textbook covers the entire subject of internal medicine and in addition includes chapters on neurology and mental diseases. Although in some instances Americans will disagree with the descriptions of clinical pictures and with recommendations for therapy, it may be regarded as a convenient reference for the British viewpoint on clinical medicine. W.S.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### RELAPSE OF PATIENTS WITH PERNICIOUS ANEMIA RECEIVING FOLIC ACID

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THE recent medical literature contains many articles which report the efficacy of folic acid in the treatment of macrocytic anemias,<sup>2,4,5</sup> the anemias of childhood with a megaloblastic bone marrow.<sup>10</sup> The refractory anemias, and leukopenic states,<sup>9</sup> in the relief of pellagrous glossitis,<sup>6</sup> and particularly in the treatment of pernicious anemia.<sup>1</sup>

When a well-recommended remedy enters the therapeutic field, a tendency soon develops to look upon it as a non-failing curative agent. This is particularly true if it is described as a specific drug for a specific disease. Many practitioners and a host of misinformed laymen believe today that folic acid is, at least, an unfailing medicine for the treatment of pernicious anemia.<sup>8</sup> This is a misconception which can lead to disastrous consequences. For this reason we report 2 patients with pernicious anemia who relapsed while receiving folic acid.

**Case Reports.** CASE 1. (Duke Unit A 57768.) A 38 year old salesman, first seen in March 1941, complaining of anemia, recognized 2 years previously. The physical examination showed a prematurely graying, well developed, well nourished, non-icteric man, with a moderate deflection of the nasal septum, with a right, indirect inguinal hernia, and a mild dermatophytosis of both feet.

There was no papillary atrophy of the tongue. The neurologic examination was entirely normal. The gastric analysis disclosed a complete lack of free HCl after the administration of histamine, a total acidity of 7°. The blood serology, the urine, the blood chemical studies, the basal metabolism and the Roentgen examinations of the chest and gastro-intestinal tract showed nothing abnormal.

*Blood Picture.* Hgb., 11.2 gm. (72%); RBC, 2,510,000; WBC, 5450; Col.In., 1.44; MCV, 130  $\mu$ ; retics., 4%; platelets normal. The patient received 1 cc. of a potent concentrated liver extract intramuscularly each day for 10 days. On the 5th day the reticulocytes were 18% of the total red cell count; the total blood values and indices were essentially the same as on admission. He was subjectively improved so that he no longer complained of weakness and fatigue. He was discharged and was advised to take 15 units of liver extract intramuscularly twice a week for 6 weeks, and oral liver extract 1 tablespoonful 3 times daily until his blood levels were normal. Since the patient's brother was a practising physician it was hoped that this plan of treatment would be carried out faithfully. The patient was readmitted to this hospital on May 27, 1946 because of a return of weakness, fatigability, exertional dyspnea and, in addition, soreness of the tongue of 6 months duration. He stated at this time that he had discontinued the use of parenteral liver extract



3 years previously, and had taken oral liver preparations only sporadically. The general examination showed that he was still well nourished; the mucous membranes were pale, the skin had a lemon yellow tint. There was still no frank jaundice, there was no evidence of bleeding, there was no atrophy of the papillae of the tongue, the heart and lungs were normal, the liver and spleen were not palpable; B.P. 100/72. The neurologic examination showed nothing abnormal.

This patient responded fairly well to 30 mg. of folic acid a day; he maintained his hemoglobin and red cell levels for 5 months on 5 to 10 mg. of folic acid a day, and then relapsed. The relapse proceeded despite increased doses of folic acid. This is shown in the following table.

TABLE 1.—BLOOD CELL DATA IN CASE 1

Date	Hgb. (gm.)	RBC (milli.)	WBC (thous.)	Hem. (vol. %)	C.I. (× 10 <sup>-12</sup> gm.)	MCHC (gm.)	MCV (cu)	Retics. (%)	Treatment
1946 5/27	9.8	2.64	4.35	29.0	1.11	37.0	110.0	4.3	
5/30	..	..	..	..	..	..	..	8.0	5/29, 10 mg. folic acid t.i.d.
5/31	..	..	..	..	..	..	..	5.0	
6/1	..	..	..	..	..	..	..	3.1	
6/3	..	..	..	..	..	..	..	2.6	
6/4	11.0	2.97	4.00	30.2	1.22	36.6	106.6	3.0	↓
6/21	14.1	4.11	10.00	43.0	1.08	34.0	104.0	3.0	6/5, 10 mg. folic acid b.d.
7/20	16.7	4.52	5.20	46.0	1.20	36.0	102.0	1.0	↓
9/27	15.7	4.50	5.60	41.0	1.10	35.0	101.0	1.5	6/28, 5 mg. folic acid q.d.
10/31	15.7	4.55	6.80	46.0	1.10	34.0	101.0	2.0	↓
1947									10 mg. folic acid q.d.
1/20	13.2	4.07	2.95	38.0	1.04	32.4	95.0	2.0	↓
1/29	13.4	3.57	3.80	38.0	1.22	32.5	106.0	1.5	15 mg. folic acid t.i.d.
2/3	12.1	2.90	3.60	32.0	1.32	36.0	110.0	1.0	↓
2/9	13.2	3.30	6.80	..	1.14	35.0	105.0	12.8	Liver extract, 15 u. a day
2/21	14.8	4.25	5.95	41.0	1.10	37.0	92.0	1.5	↓
									Liver extract, 15 u. twice a week

The bone marrow pattern was always consistent with the severity of the anemia, so that megaloblasts were present in abundance when the anemia was severe, and were sparse as the maturation of erythropoietic elements took place, and as the anemia subsided. This patient was discharged from the hospital and was instructed to take liver extract parenterally, 15 units twice a week for 3 weeks, and thereafter once a week or once every 2 weeks as necessary to maintain normal blood levels. When he was last heard from the blood levels were apparently normal, as were the indices, and a blood smear recently obtained failed to show macrocytosis.

CASE 2. (Duke Unit B 81542.) A 63 year old unemployed male who was admitted to this hospital on June 14, 1946, complaining of progressive weakness of 3

weeks duration. He was also short of breath on exertion. His appetite was good, and he denied gastro-intestinal disturbances. His tongue had been sore, off and on, for about 2 years, and he had noticed some numbness and tingling in the fingers and toes for about 3 months. He was pale and thin, the sclerae were bluish. The marginal papillae of the tongue were atrophied. The heart and lungs were normal. B.P. 110/68. The liver was not palpable, but the tip of the spleen could be felt on deep inspiration. The vibratory sense (fork No. 250) was lost below the knee on the right side, and below the ankle on the left side. The blood serology, the urine and stool were normal. The blood NPN, uric acid and Van den Bergh were not elevated.

The serum proteins were normal. Roentgen rays of the chest and of the gastro-intestinal tract were essentially normal, as was the electrocardiogram. The gastric analysis disclosed a complete lack of free HCl.

*Blood Picture* (June 15, 1946). Hgb., 4.4 gm. (28%); RBC, 1,210,000; WBC, 4000; retics., 7.1%. Anisocytosis and poikilocytosis were striking and many macrocytes were seen; there were a few erythroblasts (about 1 per 100 white cells). The differential white cell formula was normal. *Bone marrow*: The material obtained by sternal puncture was very cellular and the nucleated cell count was estimated to be 182,000 per mm.<sup>2</sup> The erythroid elements were present in tremendous numbers and were mostly erythroblasts and megaloblasts. The reticulocyte count was 8%.

This patient had never received antiperni-

cious anemia therapy. He responded well to 30 mg. of folic acid a day, so that the reticulocyte count reached 29% on the 9th day. The hemoglobin and red cell levels never approached the adequate normal with doses of 20 and 10 mg. of folic acid a day. The hematologic relapse occurred after 90 days, even though the dosage of folic acid was increased from 5 to 30 mg. a day as shown in the second table.

treatment for his pernicious anemia, and, as far as could be determined, had not been treated with liver extract. He responded well to the oral administration of folic acid. The subjective improvement was also satisfactory. However, macrocytosis again persisted and the color index, mean corpuscular volume and the mean hemoglobin content did not revert to

TABLE 2.—BLOOD CELL DATA IN CASE 2.

Date	Hgb. (gm.)	RBC (milli.)	WBC (thous.)	Hem. (vol. %)	C.I.	MCHC ( $\times 10^{-12}$ gm.)	MCV ( $\mu$ )	Retics. (%)	Treatment
1946 6/15	4.4	1.21	4.0	13.0	1.20	36.4	109.0	7.1	6/16, folic acid, 10 mg. t.i.d.
6/20	5.0	1.50	11.9	..	1.06	33.3	113.0	9.6	
6/24	6.1	1.94	4.0	20.0	1.02	30.9	103.0	29.1	
6/27	7.5	2.35	4.4	25.5	1.01	31.0	108.0	9.0	
6/29	7.6	2.66	4.4	26.0	0.94	28.5	97.7	10.0	Folic acid, 10 mg. b.d.
									7/6, folic acid, 5 mg. b.d.
									7/20, folic acid, 5 mg. q.d.
7/29	10.7	3.60	6.5	38.5	0.96	30.0	107.0	1.5	
9/30	10.0	3.56	6.7	35.5	0.99	30.0	99.0	1.5	Folic acid, 5 mg. b.d.
10/30	8.9	2.85	4.9	29.5	1.01	31.0	103.0	1.5	Folic acid, 10 mg. t.i.d.
11/9	8.4	2.59	7.1	30.0	1.04	32.0	102.0	1.0	Liver extract, 15 u. q.d.
11/14	10.8	3.46	7.9	35.8	1.00	30.0	103.0	7.5	
11/22	11.5	3.87	11.0	39.5	0.94	29.7	101.0	5.5	Liver extract, 15 u. twice a week
1947 1/29	14.5	4.35	7.2	41.5	1.07	28.0	90.0	1.5	

**Discussion.** These 2 patients were undoubtedly suffering from pernicious anemia, and the first patient had been proven previously to be responsive, clinically and hematologically, to liver fractions effective in pernicious anemia. When he relapsed, because he discontinued his anti-anemic liver extract therapy, he received folic acid and had a very satisfactory initial response. However, it is evident that the hematologic reaction never returned to normal. Although the reticulocyte reaction was adequate, and the red cell count and hemoglobin levels rose appreciably, the hematologic indices never reverted to normal, and the macrocytosis persisted. This is interesting in view of the reports of the efficacy of folic acid in patients with macrocytic anemia in relapse.<sup>3,7</sup> Furthermore, this patient continued to relapse after receiving large and increasing doses of folic acid, and then responded beautifully to 15 units of concentrated liver extract a day for 8 days.

The second patient had never received

normal. Within a relatively short time, this patient relapsed while he was receiving 5 mg. and then 30 mg. of folic acid a day. He also reacted properly to standard amounts of concentrated liver extract given parenterally.

It is apparent that in some patients the accepted dosage of folic acid will not maintain a hematologic remission. In these 2 patients the initial response to folic acid was adequate, except for the persistence of macrocytosis. The continued macrocytosis does not necessarily imply a relapse. Thirty other patients with pernicious anemia were treated with folic acid in this clinic. In these patients, the initial reticulocyte response was adequate in 17, fair in 10 and unsatisfactory in 3. Macrocytosis, as proven by the appearance of the red cells in fresh and stained smears, and by the mean corpuscular volume, persisted in a high percentage of this group. This is being reported separately.

Folic acid, administered by mouth, therefore, seems to lack some of the prop-

erties of purified liver extract administered parenterally. In 2 patients with pernicious anemia studied in this clinic, folic acid failed to maintain a remission.

**Summary and Conclusions.** 1. Two patients are reported, who were suffering from pernicious anemia, and relapsed while receiving folic acid.

2. The hematologic response after folic acid therapy in these 2 patients was not complete insofar that macrocytosis persisted and the hematologic indices remained abnormal.

3. Both patients relapsed while receiving what is regarded as adequate folic acid therapy.

4. These 2 patients showed a subsequent satisfactory response to liver extract administered parenterally in doses considered minimal for the treatment of patients with pernicious anemia.

5. Folic acid in doses generally accepted as effective will not prevent a hematologic relapse in some patients with pernicious anemia.

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## THE DIAGNOSTIC VALUE OF THE STERNAL BONE MARROW PUNCTURE IN POLYCYTHEMIA VERA

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THE diagnosis of polycythemia vera (erythremia) is not difficult when the clinical manifestations of the disease are well advanced, and abnormally high values for number of erythrocytes, volume of packed red cells and quantity of hemoglobin are found in the peripheral blood. In the early stages of the disease, however, there is no distinct borderline between the upper limits of normal values for erythrocytes in healthy individuals and the range of abnormal values for early polycythemia vera. Until a more exact definition of diagnostic criteria for the recognition of the early phases of the disease can be established, the diagnosis of these early cases must often remain speculative until the course of the disease reveals its true nature. An evaluation of the sternal marrow puncture as an aid in the diagnosis of polycythemia vera therefore seemed desirable.

**MATERIAL.** The clinical records and sternal bone marrow material of the Hematology Laboratory, Duke Hospital, was studied from all patients with the diagnosis of polycythemia vera. The cases were considered in 3 groups: (1) polycythemia vera; (2) suspected polycythemia vera; and (3) normal controls.

In Group 1 there are 22 patients in whom the diagnosis of polycythemia vera seemed clearly established on the basis of clinical, hematologic and other laboratory data. Some of this information is tabulated in Table 1. These patients, in general, had values ranging consistently above 6,000,000 per c.mm. for erythrocytes, above 18 gm. per 100 cc. for hemoglobin, and above 50 cc. per 100 cc. for volume of packed red cells. The clinical findings and course of the disease while under observation were thought typical of either essential polycythemia with splenomegaly

or polycythemia with hypertension (Gaisböck's syndrome).

Group 2 includes 29 patients in whom a diagnosis of polycythemia vera was made or seriously considered, so much so that several patients in this group were treated by venesection or by irradiation using "spray" technique. Some of the clinical and laboratory data on this group are tabulated in Table 2. In most instances, however, this group of patients failed to maintain values for hemoglobin, number of erythrocytes and volume of packed red cells which were consistently above the upper ranges of normal values during the periods under observation. In addition, splenomegaly, hepatomegaly, plethoric appearance and other clinical features of polycythemia vera were often lacking. These patients appear to represent a mixed, borderline group including individuals with early polycythemia vera, normal individuals with values for erythrocytes, hemoglobin and volume of packed cells at the upper limits of normal range, and individuals with mild erythrocytosis of undetermined cause. Patients with demonstrable causes for erythrocytosis, such as heart disease, pulmonary disease and anoxemia from other conditions, were excluded from the study.

Group 3 represents a control group of 50 normal medical students and technicians ranging in age from 19 to 35 years. The peripheral blood data on this group was within normal range. Since the studies of several investigators<sup>5</sup> vary widely for normal values for sternal marrow, it was felt advisable to establish, for purposes of comparison, the normal values for sternal marrow by the techniques employed in this clinic.

**Methods.** The technique of sternal bone marrow puncture was uniform in all cases.

A No. 18 spinal puncture needle was introduced vertically into the body of the sternum between the levels of the second and third ribs under procaine anesthesia, and 1 cc. or less of sternal marrow was aspirated into a dry syringe. Smears were made immediately from oxalated marrow specimens in most of the earlier cases. Later, smears were made directly from fresh marrow from the sternal puncture needle at the bedside. The fixed smears were stained with a modification of Wright's stain. Counts of the total nucleated marrow cells were made and the total values of white blood cells calculated. Reticulated

counts were made by the wet film technique. In almost all cases, the total counts and differential counts were made by the same experienced hematologic technician.

The limitations in the technique of sternal bone marrow puncture and the wide variations and different interpretations of the results are too well known to require elaboration. It is generally conceded that the sternal marrow puncture offers a safe clinical means by which valuable knowledge of bone marrow function may be secured.

TABLE 1.—SUMMARY OF DATA, INCLUDING PHYSICAL FINDINGS AND MAXIMAL OBSERVED VALUES IN THE PERIPHERAL BLOOD, IN 22 CASES OF POLYCYTHEMIA VERA

Case No.	Sex	Age	Plethoric appearance	Spleno-megaly	Hepato-megaly	Blood pressure	R.B.C. (mill. per c.mm.)	Hb. (gm.)	Vol. packed cells (%)	W.B.C. (thous. per c.mm.)
1	M	57	+++	++++	++	110/90	9.95	25.6	58.0	21.35
2	F	38	++	++++	++++	130/100	8.0	21.0	64.0	17.8
3	F	72	+++	++	+++	140/86	8.28	22.5	65.0	20.8
4	M	52	+++	++++	++++	110/62	8.09	26.0	69.7	8.75
5	M	52	+++	++++	++++	118/88	7.66	16.1	53.4	34.0
6	M	39	++	+	+++	112/74	6.76	20.8	49.0	10.3
7	M	65	+++	++++	++	125/80	8.8	19.4	58.9	55.0
8	M	47	+++	0	+	150/82	6.83	21.2	56.7	11.3
9	M	47	+++	+++	+	132/86	8.75	23.0	80.8	9.0
10	F	53	+	0	+	230/126	7.0	22.0	63.2	10.44
11	F	42	+++	+	++++	236/148	6.64	20.3	64.0	16.0
12	M	48	++	++++	++++	190/128	6.64	20.0	56.0	8.2
13	M	30	+++	++++	+	140/90	8.76	25.5	67.6	15.65
14	M	58	++++	++++	++	148/86	8.0	21.1	57.7	20.0
15	M	24	+++	0	0	200/120	7.8	20.0	61.0	21.76
16	M	18	++	0	0	120/80	7.03	20.5	56.7	22.8
17	M	42	+++	0	+	150/100	6.68	24.8	75.2	9.8
18	M	47	+++	0	+	180/120	6.05	19.0	52.0	19.1
19	F	45	+++	++++	+++	160/80	9.05	25.0	83.9	17.4
20	F	51	+	+++	+++	110/70	7.04	17.0	51.23	11.0
21	M	68	+++	+	+++	145/94	7.79	19.0	60.9	21.8
22	M	35	+++	0	0	136/78	6.98	15.5	49.0	17.2

TABLE 2.—SUMMARY OF DATA, INCLUDING PHYSICAL FINDINGS AND MAXIMAL OBSERVED VALUES IN PERIPHERAL BLOOD, IN 29 CASES OF SUSPECTED POLYCYTHEMIA VERA

Case No.	Sex	Age	Plethoric appearance	Spleno-megaly	Hepato-megaly	Blood pressure	R.B.C. (mill. per c.mm.)	Hb. (gm.)	Vol. packed cells (%)	W.B.C. (thous. per c.mm.)
1	M	47	++	0	0	120/80	6.29	20.2	50.4	9.20
2	M	41	++	0	0	140/90	6.49	18.2	53.0	6.49
3	M	36	+	0	0	110/80	6.0	18.6	57.0	11.30
4	M	33	+	++	0	130/78	5.85	17.5	53.0	13.05
5	M	37	++	0	0	120/70	6.64	18.0	51.23	11.55
6	M	64	+++	+	+++	160/102	5.77	17.3	..	6.95
7	M	28	0	0	+++	138/80	6.01	19.0	47.9	9.4
8	M	37	0	0	++	130/78	6.06	18.6	47.41	15.45
9	M	42	0	0	+	112/50	7.82	17.8	60.0	10.25
10	F	38	+++	0	0	150/90	5.85	19.0	4.4	15.7
11	M	55	+++	0	+++	150/85	6.04	18.8	50.0	9.5
12	M	65	0	0	0	112/70	6.12	19.0	54.5	11.2
13	M	48	++	++	++	170/110	6.27	19.5	55.0	11.15
14	M	38	0	0	0	125/80	5.45	17.2	53.0	10.75
15	F	30	++	0	0	130/80	6.99	21.0	51.2	12.3
16	M	38	0	0	0	134/86	6.31	18.0	50.1	15.52
17	M	47	+	0	+++	140/80	5.56	17.3	..	8.75
18	M	43	+	0	+++	130/78	6.14	18.4	46.9	18.0
19	M	46	++	0	+++	138/96	5.97	19.2	51.0	13.15
20	M	39	0	0	0	130/86	5.28	16.1	48.0	16.5
21	M	26	+++	0	0	126/84	6.58	16.5	50.0	4.75
22	M	38	0	0	0	114/70	6.32	19.2	50.0	9.0
23	M	39	+	+	+	130/90	6.12	21.6	57.2	10.6
24	M	42	+	0	0	118/80	5.84	17.5	55.0	9.16
25	M	32	0	0	0	158/102	5.9	18.4	52.32	8.3
26	M	39	+	0	+++	120/80	6.09	19.0	49.0	9.1
27	M	69	+	0	++	210/130	5.72	18.0	53.0	11.9
28	M	38	+	0	++	180/124	6.23	19.1	58.8	9.1
29	M	19	0	0	0	180/120	5.95	19.0	54.5	10.45

RESULTS. The morphology of the sternal marrow of the 3 groups of cases was analyzed on the basis of comparative levels of total nucleated cells, total white cell count, differential counts on the white cell series, differential counts on the erythroid series, myeloid-erythroid ratios, and percentage levels of reticulocytes (see Tables 1 to 8).

Absolute counts of marrow cells are

microscopic field, or by actual count of the nucleated elements. In various hematologic disorders, the nucleated cells of the marrow are found to be increased or decreased beyond the average levels found in normal individuals. It is of considerable importance for clinical analysis to determine whether these variations from the normal involve the white cell series, the erythroid series, or both.

TABLE 3.—TOTAL NUCLEATED CELL COUNT IN STERNAL MARROW IN POLYCYTHEMIA VERA, SUSPECTED POLYCYTHEMIA, AND NORMAL INDIVIDUALS

	Group 1	Group 2	Group 3
Total nucleated count (thous. per c.mm.)	Polycythemia vera (% at level indicated)	Suspected polycythemia vera (% at level indicated)	Normal controls (% at level indicated)
0-10 . . . . .	8.0	3 4	4.0
11-20 . . . . .	16.0	6.6	14.0
21-30 . . . . .	0	16.6	14.0
31-40 . . . . .	20.0	23.4	24.0
41-50 . . . . .	16.0	6.6	12.0
51-60 . . . . .	8.0	16.6	12.0
61-70 . . . . .	8.0	10 0	4.0
71-80 . . . . .	0	3 4	6.0
81-90 . . . . .	12.0	0	0
91-100 . . . . .	8.0	6.6	6.0
101-110 . . . . .	4.0	3 4	0
111-120 . . . . .	0	3 4	0
121-130 . . . . .	0	0	0
131-140 . . . . .	0	0	4.0

TABLE 4.—TOTAL WHITE CELL COUNT IN STERNAL MARROW IN POLYCYTHEMIA VERA, SUSPECTED POLYCYTHEMIA VERA, AND NORMAL CONTROLS

	Polycythemia vera	Suspected	Normal controls
Total white cell count (thous. per c.mm.)	(% at level indicated)	polycythemia vera (% at level indicated)	(% at level indicated)
0-10 . . . . .	11.5	3.3	4.0
11-20 . . . . .	11.5	23.4	18.0
21-30 . . . . .	23.1	20.0	20.0
31-40 . . . . .	23.1	13.4	24.0
41-50 . . . . .	3.9	13.4	16.0
51-60 . . . . .	7.6	10.0	4.0
61-70 . . . . .	11.5	3.3	0
71-80 . . . . .	3.9	6.6	10.0
81-90 . . . . .	3.9	0	0
91-100 . . . . .	0	6.6	0
101-110 . . . . .	0	0	2.0
111-120 . . . . .	0	0	0
121-130 . . . . .	0	0	2.0
131-140 . . . . .	0	0	0

subject to wide fluctuations due to technical reasons, even in normal individuals, and are generally conceded to be of little value. To judge hyperplasia of the bone marrow cells, some reliance must be placed on the relative members of nucleated cells in the marrow specimen, whether this be based simply on visual impressions of number of nucleated cells in studying a

Comparative studies of the total nucleated cells and of the total white cells are tabulated respectively in Tables 3 and 4. Study of Table 3 shows no great differences in the 3 groups of individuals as far as the total nucleated counts in the sternal marrow are concerned. The percentage ranges are comparable. In the polycythemia vera group 60% had total nucleated cells below

50,000 per c.mm. of sternal marrow as compared with 68% in the controls and 56.6% in the borderline group. The maximum recorded level in the polycythemia group was 107,000 nucleated cells per c.mm. as compared to 138,000 in the normals and 120,481 in the borderline group. There is no evidence in these cases that the total number of nucleated cells per c.mm. in the sternal marrow of patients with polycythemia vera varies in any significant way from the normal range.

Study of Table 4 reveals no appreciable significant differences in the range of total white cells per c.mm. in the sternal marrow of the 3 groups. The polycythemia group and the borderline group had 73.1 and 73.5% respectively with total white counts of 50,000 or less per c.mm., of sternal marrow whereas 82% of the normal group were within this range. The maximum white count recorded in the normal group was 121,440 per c.mm. as compared with maximums of 100,000 in the borderline group and 81,320 in the polycythemia vera group. The studies tabulated here would seem to indicate that there is no relative increase in the total number of white blood cells per c.mm. of sternal marrow in polycythemia vera.

Analysis of the differential counts of the white blood cell series in the sternal marrow of the 3 groups (Table 5) reveals rather striking similarities both in regard to percentage range and average percentages. The only significant difference between the control group and the polycythemia vera group is in the percentage of segmented neutrophils. These cells are more numerous in the polycythemia group, apparently with a slight reduction in the percentage of "undifferentiated" and neutrophilic myelocytes, as compared with the normals. As might be expected, the borderline group of cases shows average values intermediate between those of the normals and the polycythemia group. These findings would seem to be in accord with the neutrophil leukocytosis so com-

monly found in the peripheral blood of patients with polycythemia vera.

Differential studies on the erythroid series (Table 6) reveal a moderate but definite increase in the average as well as the range of values for erythroblasts per 100 white cells counted in the polycythemia group as compared to the normals. The borderline group again occupies an intermediate position. This would appear to indicate a moderate increase in the activity of the erythroid series at the erythroblastic level in the polycythemia vera group, and to a less extent, in the borderline group. Average values for the other nucleated erythroid elements are not significantly different. In general, the total number of nucleated red cells per 100 white cells is significantly elevated in the polycythemia group as compared to the normal group, as shown by an average figure of 31.7 nucleated red cells per 100 white cells counted in the polycythemia group as compared to 15.76 in the normal group, and 21.2 in the borderline group. Further evidence of a moderate but definite increases in the activity of the erythroid series in polycythemia vera is found in Table 7, indicating a generally higher average level of reticulocytes in the sternal marrow of polycythemia vera than in that of normal individuals.

Study of the myeloid-erythroid ratio in the 3 groups (Table 8) reveals a definite rise in the proportion of erythroid cells to myeloid cells in the polycythemia vera group. In this group 56% of the patients showed myeloid-erythroid ratios of 2.9:1 or below as compared with 14.2% at this level or below in the normals and 25.8% in the borderline group. Taking 4 or 5 to 1 as the usual adult ratio, 76% of the polycythemia group are found to have ratios lower than 4.9:1, as compared with 61.3% in Group 2 and 42.6% in the normals. The range of myeloid-erythroid ratios in the normal controls was greater than in either of the other 2 groups, possibly to be attributed to the lower average ages of the group.

Megakaryocyte values could not be determined satisfactorily on smears made from oxalated marrow. Instances with extremely large numbers of megakaryocytes in the marrow have been recorded,<sup>1</sup> but this is not a constant finding. Increase in the platelets of the blood was not noted in any of the cases studied in Groups 1 or 2.

**Discussion and Conclusions.** On the basis of the study of the sternal bone mar-

row in these groups, it seems apparent that certain definite patterns may be found in the sternal marrow of patients with polycythemia vera: (a) The bone marrow as obtained from the sternum may be and frequently is entirely within the limits found in healthy normal individuals, suggesting that the bone marrow actually is entirely normal or, if hyperplasia exists, there is no variation from

TABLE 5.—ANALYSIS OF DIFFERENTIAL PERCENTAGES OF WHITE BLOOD CELLS IN POLYCYTHEMIA VERA, SUSPECTED POLYCYTHEMIA, AND NORMAL CONTROLS

	Group 1		Group 2		Group 3	
	Polycythemia vera		Suspected polycythemia		Normal controls	
	Average	Range	Average	Range	Average	Range
Polymorph neutrophil, segs. . . . .	44.3	22-80	36.47	18-55	31.9	13-55
Polymorph neutrophil stabs. . . . .	15.2	2-32	16.68	1-25	17.9	2-44
Polymorph neutrophil juveniles . . . . .	9.2	0-22	10.71	1-23	11.8	1-21
Polymorph eosinophil . . . . .	2.6	0-7	2.46	0-8	2.9	0-15
Polymorph basophil . . . . .	0.76	0-2	0.41	0-2	0.44	0-2
Myelocytes, "undifferentiated" . . . . .	2.5	0-17	2.22	0-5	5.96	0-15
Myelocytes, neutrophil . . . . .	3.8	0-19	3.65	0-13	8.0	0-16
Myelocytes, eosinophil . . . . .	0.57	0-2	0.78	0-6	0.66	0-1
Myelocytes, basophil . . . . .	0.04	0-1	0.19	0-3	0.06	0-1
Myeloblasts . . . . .	1.2	0-3	0.72	0-3	1.46	0-4
Lymphocyte, small . . . . .	11.6	0-31	17.12	8-38	14.08	2-35
Lymphocyte, large . . . . .	2.3	0-9	4.81	0-20	3.36	0-11
Lymphocyte, early . . . . .	0.07	0-1	0.12	0-1	0.02	0-1
Monocyte . . . . .	2.1	0-6	2.84	0-6	2.80	0-11
Monoblast . . . . .	0.04	0-1	0	0	0.02	0-1
Plasma cell . . . . .	0.31	0-5	0.53	0-7	0.18	0-3

TABLE 6.—NUCLEATED RED BLOOD CELLS PER 100 WHITE CELLS COUNTED IN MARROW OF POLYCYTHEMIA VERA, SUSPECTED POLYCYTHEMIA, AND NORMAL CONTROLS

	Group 1		Group 2		Group 3	
	Polycythemia vera		Suspected polycythemia vera		Normal controls	
	Average	Range	Average	Range	Average	Range
Normoblasts . . . . .	3.3	0-12	2.38	0-6	2.28	0-31
Erythroblasts . . . . .	28.2	1-69	18.29	5-71	13.2	3-43
Megakoblasts . . . . .	0.2	0-2	0.53	0-16	0.26	0-2
Hemohistiocytes . . . . .	0	0	0	0	0.02	0-1

TABLE 7.—PERCENTAGE OF RETICULOCYTES IN STERNAL MARROW OF POLYCYTHEMIA VERA, SUSPECTED POLYCYTHEMIA, AND NORMAL CONTROLS

	Group 1		Group 2		Group 3	
	Polycythemia vera		Suspected polycythemia vera		Normal controls	
	Average	Range	Average	Range	Average	Range
Reticulocytes . . . . .	3.02	0-6	2.60	0.5-10	1.87	0-6

TABLE 8.—THE MYELOID-ERYTHROID RATIO OF STERNAL MARROW IN POLYCYTHEMIA VERA, SUSPECTED POLYCYTHEMIA, AND NORMAL CONTROLS

Myeloid-erythroid ratio	Polycythemia vera (% at level indicated)	Suspected polycythemia vera (% at level indicated)	Normal control- (% at level indicated)
0-0.9:1 . . . . .	0	0	0
1-1.9:1 . . . . .	28.0	12.9	6.1
2-2.9:1 . . . . .	28.0	12.9	8.1
3-3.9:1 . . . . .	8.0	12.9	18.2
4-4.9:1 . . . . .	12.0	22.6	10.2
5-5.9:1 . . . . .	12.0	12.9	10.8
6-6.9:1 . . . . .	0	9.7	6.1
7-7.9:1 . . . . .	8.0	3.2	10.2
8 or more:1 . . . . .	4.0	12.9	30.3



the normal in the proportions of the cellular elements. (b) The bone marrow frequently shows definite variation from the normal in the proportions of cellular elements, *i. e.*, an increase in the number of nucleated red blood cells per 100 white cells counted, particularly in the number of erythroblasts, an increased number of reticulocytes, an increase in the proportion of erythroid cells to myeloid cells, and an increase in the relative numbers of segmented neutrophils. It is probable, but not a certainty, that the sternal marrow myelogram in these cases is representative of marrow cellular patterns in other locations in the body, but this can be determined only by adequate simultaneous examination of bone marrow from different locations in the body and remains a problem for further study.

Since there is no satisfactory means of determining the total volume of the bone marrow in living subjects, a clinical diagnosis of hyperplasia of the bone marrow in polycythemia vera can be made only by the demonstration of variations in the cellular morphology of the marrow suggesting hyperactivity, or by the demonstration of red bone marrow in locations where it does not normally appear in adults. The latter method is not clinically practical during the patient's lifetime. The marrow examination therefore seems to have diagnostic value in polycythemia vera only when the above-mentioned pattern (b) exists. This pattern, however, occurs with sufficient frequency to be of practical diagnostic value when present.

In the polycythemia vera group of 22 cases, 8 (Cases 1, 2, 4, 5, 9, 12, 14 and 15) showed a pattern believed to be characteristic of polycythemia vera when present, consisting of values of nucleated red cells of 20 or more, reticulocyte counts of 2% or higher and myeloid-erythroid ratios of 3:1 or below. In 5 of these 8 patients the nucleated red cell count per 100 white cells was above 40. In the remaining 14 cases of polycythemia vera, 1 or more components of the pattern were

found in 9 cases as follows: nucleated red cell counts of 20 or more per 100 white cells were counted in 4, reticulocyte counts of 2% or higher in 4, and myeloid-erythroid ratios below 3:1 in 2 instances.

In the borderline group of 29 cases, no case presented the complete characteristic pattern, but nucleated red cell counts of 20 or more per 100 white cells counted were found in 8, reticulocytic counts of 2% or higher in 9, and myeloid-erythroid ratios of 3:1 or below in 6. In the control group of 50 cases, the complete pattern was found in 3 cases only, and in 1 of these the increased nucleated red cell count was attributed to an increase in normoblasts rather than erythroblasts, the cause for which was not apparent. In 7 other control cases, nucleated red counts of 20 or more per 100 white cells counted were found, but in only 2 of the 7 cases were counts exceeding 30 found. Reticulocyte counts of 2% or higher were found in 7 control cases, and myeloid-erythroid ratios of 3:1 or below occurred in 4 instances.

In individuals with values for hemoglobin, erythrocytes and volume of packed cells above the normal range for healthy individuals and in whom causes of secondary erythrocytosis can be excluded, the finding in the sternal marrow of a count of 20 or more nucleated red blood cells per 100 white cells, principally consisting of erythroblasts, a reticulocyte count of 2% or higher, and an increased ratio of erythroid cells to myeloid cells (myeloid-erythroid ratio of 3:1 or lower) should suggest a diagnosis of polycythemia vera. The presence of an increased percentage of segmented neutrophils is also helpful in the diagnosis. It is to be stressed, however, that the examination of the sternal marrow in polycythemia vera is a useful diagnostic supplement only, and that these variations from normal are of value when supporting polycythemic changes found in the peripheral blood.

**Summary.** 1. Comparative studies of marrow material obtained by sternal bone

marrow puncture in 22 cases of polycythemia vera, 29 cases of suspected polycythemia, and 50 normal individuals were made in an effort to determine whether recognizable abnormalities in the sternal marrow were present or not.

2. No significant differences were found in the total counts of nucleated cells or of white blood cells in the 3 groups.

3. Significant increases in the average values of segmented neutrophils, nucleated red blood cells, particularly erythroblasts, and reticulocytes were found in the sternal marrow of the polycythemia vera group, as compared with the normal group, with intermediate increases in the group of borderline cases.

4. The ratio of erythroid to myeloid

cells was frequently increased in the polycythemia vera group.

5. A diagnosis of polycythemia vera should be suggested by a sternal bone marrow cellular pattern in which the values of nucleated red cells, principally erythroblasts, exceeds 20 per 100 white blood cells counted, in which the value of reticulocytes exceeds 2% and the value of myeloid-erythroid ratios is below 3:1 in individuals with values of hemoglobin, erythrocytes and volume of packed red cells above the upper limits of normal for healthy individuals and in whom causes of secondary erythrocytosis can be excluded. Polycythemia vera may, however, exist with entirely normal bone marrow morphology.

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## ANEMIA AND ITS RELATION TO DIAPHRAGMATIC HERNIA

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OBSERVATIONS on the medical service of the Indiana University Medical Center have led to the study of anemia and diaphragmatic hernia. That anemia is a symptom of this clinical condition has been appreciated, but the relative frequency of this clinical finding has not until recently been known. The work of Murphy in 1942, reporting 47 cases of anemia in a series of 67 cases, a total of 66.7%, stimulated the study of anemia in this series.

**HISTORICAL.** The literature since 1920 shows a gradually increasing number of articles referable to diaphragmatic hernia and anemia. The condition of diaphragmatic hernia through the esophageal hiatus has become a clinical entity, and it is a frequent observation that a secondary anemia or history of gastro-intestinal bleeding may occur in the course of a persistent or recurrent hiatus hernia. However, the frequency with which anemia is associated, or the percentage in which it is seen in reported series of diaphragmatic hernia, has not until recently been the subject of clinical reports.

In the *Annals of Surgery* in 1918, William A. Downes<sup>2</sup> reported a case of a 7 year old boy with a thoracic stomach who had a red blood count of 3.4 million and a hemoglobin of 65%. There were no remarks concerning the anemia but, outside of the traumatic herniae associated with the war surgery, this case report is one of the first which mentioned the blood count in association with this condition. In the same journal, the next year, A. L. Soresi<sup>20</sup> reported 3 cases, 2 traumatic, in soldiers, and 1 non-traumatic in a 19 year old girl. The statement concerning the

girl was that her chief complaint was an anemia which was unexplained on the basis of visible blood loss. In the early 1920's, L. Frank<sup>6</sup> reported 1 case without a history of bleeding which showed a diminution of red corpuscles and a hemoglobin of 17%. No further statement was made concerning the anemia. Portis and Portis<sup>15</sup> in 1920 reported 1 case of diaphragmatic hernia and in the discussion of the case reported hematemesis was also a symptom of this condition.

In 1929, E. P. Richardson<sup>16</sup> reported anemia in 3 of the 5 cases operated, but we do not have the total number of cases which were used to choose those which were operated upon. Segal,<sup>19</sup> in 1931, reported 5 cases with symptoms of anemia only, and 5 cases of gastro-intestinal symptoms also, concluding that in the symptomless case of secondary anemia it is important to look for a diaphragmatic hernia. Weitzen,<sup>21</sup> in 1932, reported the cases of severe anemia found in Harrington's operated series of 30. In 1933, K. D. Gardner<sup>7</sup> reported 22 previously published and 6 previously unpublished cases of diaphragmatic hernia with anemia. He stated that hernia was the primary factor in anemia in 8 cases and that true peptic ulcer was a complicating factor in 5. In the anemia of the other 12 cases, he allows only the supposition that the anemia was caused by the hernia. Bock, Dulin and Brooke<sup>1</sup> in their 10 cases of hernia with anemia substantiated the hernia as the cause of the anemia by autopsy findings in 2, and operative findings in 3, 50%. Winans,<sup>22</sup> in reporting the syndrome of kyphosis, gastric hernia and anemia, states that, from considera-

tion of his cases, gastric hernia must be listed and looked for as a cause of persistent hypochromic anemia. The French literature has several articles which refer to a form of diaphragmatic hernia spoken of as the anemic form. The number of instances of cases of anemia in diaphragmatic hernia, with or without the history of bleeding, are reported but the incidence is not found.

**CLINICAL.** The incidence of hiatus hernia has been variously reported in different series as between 2.4 and 9% of routine series of Roentgen ray examinations of the gastro-intestinal tract. Harrington found that in 5% of 100 consecutive laparotomies he was able to palpate or to put 3 to 4 fingers into the hiatal aperture, and concluded that this percentage could have a diaphragmatic hernia. The condition occurs twice as frequently in females as in males, this being correlated in all of the series of cases reported.

The etiology of hiatus hernia is a large aperture in the diaphragm which may be either congenital, traumatic or a potentially large aperture in one of the hiatal openings plus weakened musculature about the hiatus. Granting that traumatic and congenital herniæ of the diaphragm are responsible for a part of the incidence of this disease, it has been shown more frequently in recent years that the greater percentage of cases of diaphragmatic hernia occur because of a potentially large hiatal ring affected by weakened musculature and nervous or pressure influences upon this potential opening. It is an established fact that persistent irritation of the vagus causing contraction and subsequent shortening of the esophagus on a traction basis produces some of the small esophageal hiatus herniæ, especially of the recurrent type, and that increased intra-abdominal pressure as pregnancy, constipation, adiposity, or external blows on the abdomen may cause a pulsion type of hiatus hernia.

The etiology of anemia in diaphragmatic hernia is the loss of blood from the gastro-

intestinal tract. In most cases, congestion or erosion of the gastric mucosa occurs proximal to the constricting ring of the hernia. Occasionally actual ulcers found in the mucosa of the herniated gut have been reported at postmortem, at operation and at gastroscopy. However, there seem to be as many cases of hernia without evidence of active bleeding as there are those which show the bleeding points. The French authors postulate the etiology of the anemia in the absence of actual bleeding points on the inability to absorb iron or on some change in the extrinsic factor responsible for a hypochromic anemia. Dyke and Dyas<sup>3</sup> report extraordinary response to iron therapy in their cases which would be against Goodall and Hoyt's assumption of bleeding from the gastric mucosa and more for Gardner's obscure changes giving deficient absorption of iron. Most of the literature from this country explains anemia in diaphragmatic hernia on hemorrhage and associated ulcers or slow blood loss due to a congested mucous membrane.

The clinical manifestations of diaphragmatic hernia may be protean or absent. The symptoms and clinical picture depend upon the morbid anatomy in each case. The symptoms depend upon the degree and the disturbance of function of nearby organs. There may be thoracic, abdominal, or constitutional symptoms, the latter which are on the basis of anemia, and which are occasionally associated with the disease. The symptoms are intermittent and usually not progressive. The gastro-intestinal symptoms are often vague in early and middle life but become persistent in later life, as the relaxation in the musculature about the hiatal ring increases. Gastro-intestinal symptoms vary and may simulate ulcer, gall bladder disease, cardiac spasm and other similar abdominal conditions. The thoracic symptoms, when they occur, are anginal in character and may simulate true angina pectoris. The angina occurs after meals or on exertion or on lying down with a full stomach. Dyspnea, perspiration, vertigo, bradycardia and ex-

trastystoles are other symptoms referable to the thoracic group of complaints.

Considering the general symptoms of hiatus hernia, it is to be remembered that frequently this finding is incidental and not the cause of the patient's illness. This was most strikingly shown by Harrington<sup>19</sup> who reported cholecystitis, peptic ulcer, diverticulitis and carcinoma of the stomach or esophagus as associated conditions. However, he also reported that of the 60 cases operated in his series between 1925 and 1933, 29 had been treated for gall bladder disease with 13 having had gall bladder operations; 23 had been treated for stomach trouble; 18 had been treated for ulcer; 7 had been treated for heart disease, 4 of whom had angina pectoris; 7 had been treated for secondary anemia; 4 for intestinal obstruction and 10 had been treated for esophageal obstruction. The general symptoms of this disease are pressure in the epigastrium on eating, spasm in the esophagus causing retrosternal pain and easy vomiting which induces relief. Vague epigastric distress or substernal distress after a meal may radiate to the back or to the left shoulder. Heartburn and postprandial distress are severe and there may be pain on lying down or on stooping. The epiphrenal syndrome of von Bergmann is quite characteristic of this disease; the fullness after a heavy meal and vomiting *versus* no trouble on the taking of small amounts of food should make one consider such a diagnosis. There may be gross hematemesis and severe melena if bleeding is present and severe. The symptoms may occasionally be confused with a functional neurosis or the menopausal syndrome.

History of hemorrhage from the stomach, though it is one of the less common symptoms, is one which deserves much consideration and evaluation. Not all of the cases of hernia have hemorrhage or hematemesis as a symptom and not all of these are anemic, but, when hemorrhage is severe, exsanguination and shock may mean the immediate treatment of any bleeding peptic ulcer. With a history of hemorrhage,

it is important to ascertain whether there is occult blood in the stool so that one can determine whether the anemia is due to unrecognized bleeding. Eisen,<sup>4</sup> in his review of the literature of esophageal hiatus hernia, states that secondary anemia associated with hematemesis or melena is occasionally present, but that the anemia may come on in intermittent attacks and symptoms of the anemia may be present at one period and absent at another time. Segal,<sup>19</sup> in an article reporting secondary anemia associated with diaphragmatic hernia, stated that there were over 400 articles on hiatus hernia in the literature but only approximately 10 which noted anemia as one of the symptoms or complications. Weakness, anorexia, pallor, exertional dyspnea are usually the constitutional effects produced by the secondary type of anemia seen in this hernia. The bleeding may be frank hematemesis or melena, or it may be insidious and found only by chemical analysis of the stool or gastric contents. When anemia is present, it is important to rule out associated disorders in other parts of the gastrointestinal tract which may be of more importance than the hernia. Murphy<sup>14</sup> was the first to include or report cases of pernicious anemia in his series of diaphragmatic hernia. No other mention in the literature is made of the pernicious anemia, all cases reported being of a secondary hypochromic type. He does state that the gastric analysis is not a reliable test in herniae because the tube may not be completely swallowed into the stomach and no free gastric acidity found. Also, trauma in passing the stomach tube may give a false positive Gregerson test and give an incorrect interpretation of bleeding by this method.

**REPORTED SERIES.** The reported series is a compilation of the cases which were found in the medical records of the Indiana University Medical Center coded as diaphragmatic hernia. There were very few cases found in comparison to the reported incidence of this condition because it is believed the incidental finding of a hiatus

hernia escaped coding where there was a more important primary diagnosis. To include as many cases as possible, the files of the Roentgen ray Department were also inspected, and cases having films reported as showing a diaphragmatic hernia were also included in the series. A total of 41 cases are reported in which the evaluation of anemia was made. There were 27 females and 14 males, which is in accord with the accepted predominance of females over males. The ages ranged from 3 weeks to 75 years. There were 3 cases under 5 years of age, 1 between 5 and 10, 2 between 10 and 20, 1 between 20 and 30, 3 between 30 and 40, 7 cases between 40 and 50, 8 between 50 and 60, 9 between 60 and 70 and 7 over 70. The average age in this series was 50.3 years.

Thirty of the cases showed herniation of the stomach alone, the other 11 cases having herniation of the stomach plus other abdominal viscera; colon, spleen, omentum, small intestine or combinations of the abdominal organs.

Thirty-four of the cases showed the herniation through the esophageal hiatus, 2 were found to be herniation through the foramen of Morgagni and 5 were due to large defects in the posterior leaf of the left diaphragm communicating with the esophageal hiatus.

Clinically, our cases have been divided into those patients who were admitted to the hospital for treatment of a known diaphragmatic hernia and those who were admitted for other causes where the hernia was an incidental finding or a secondary diagnosis. There were 28 cases admitted primarily for diaphragmatic hernia and 13 cases admitted for other causes. Because the hospital is a state institution and accepts a large number of referred cases for specific therapy, there is a higher incidence of cases admitted primarily for diaphragmatic hernia than is reported by other authors. According to other workers, there should be a higher incidence of hiatus hernia found coincidentally with other disease or as an incidental finding in routine gastro-intestinal work-ups.

In our series, the etiology was considered to be a traumatic episode, auto accident, causing a pulsion hernia in 3 patients. The etiology in 4 patients was definitely congenital in origin, all occurring in young children. The other 34 cases could not be assigned a definite etiology from a survey of the records and must be assumed to be due to an enlarged hiatus ring with or without weakened musculature about the hiatal orifice.

Thirty patients in the group under investigation had definite symptoms referable to the hiatus hernia. These were at times not the only symptoms complained of and sometimes not the most important, but in all of the 30 cases complaints referable to a diaphragmatic hernia were listed in the medical record. Eight patients had no symptoms referable to a defect in the diaphragm and the finding was only incidental during the period of hospitalization. Three cases were excluded in the evaluation of symptomatology because the history was discounted in the face of generalized advanced carcinoma of the abdomen. The hernia is found associated with many other clinical conditions and, in our series, pregnancy, gall bladder disease, asthma, hypothyroidism, peptic ulcer, hemorrhoids, coronary disease, fractured vertebrae and von Recklinghausen's disease were some of the primary diseases with the hernia as the associated condition.

Treatment of the diaphragmatic hernia was a medical management or no specific therapy in 22 of our cases; 19 were subjected to operative procedure, the surgical repair being complete in 9 and apparently successful. Three other cases have had recurrences. In 6 cases it was impossible to make a satisfactory closure of the large defect in the diaphragm, and the hernia was still present postoperatively. There was 1 postoperative mortality.

Anemia in diaphragmatic hernia is extremely variable and so statistics have been compiled in 2 categories to better evaluate a definite relationship or only an occasional association in this condition. Some authors have reported a history of

bleeding or known blood loss in their series of cases of esophageal hiatus hernia. Notable among these are Akerlund, Harrington, Jones, Sahler and the Massachusetts General Hospital series reported by Hapton and Sahler. Sahler and Hapton,<sup>17</sup> in the *American Journal of Roentgenology* in 1943, compiled various statistics from

TABLE 1.—HISTORY OF BLEEDING

Authors	Total cases reported	Cases with bleeding history	% showing bleeding
Akerlund . . . . .	64	3	4.7
Harrington . . . . .	30	8	26.6
Hedblom . . . . .	397	10	2.5
Mass. Gen. Hosp. . . . .	221	28	12.6
Sahler . . . . .	9	3	33.3
Jones, C. M.: Small . . . . .	91	22	24.0
Large . . . . .	37	6	16.2
I. U. Med. Center . . . . .	41	8	19.5

the literature. They stated that Akerlund, in 64 cases, had 3 who vomited blood or had obvious bleeding and that this was the first correlation between hiatus hernia and bleeding. Hedblom,<sup>11</sup> in 1925, reported 19 cases from the Mayo Clinic series and collected 378 additional cases from the literature and, in describing the syndrome, mentioned that in the Mayo series, hematemesis was the most prominent symptom in 2 and in the cases collected from the literature, 8 complained of hematemesis. Boch, in 1929, was the first American to emphasize gastro-intestinal hemorrhages and hiatus hernia. Harrington,<sup>9</sup> in 1930, reported 30 cases, 8 of which had hemorrhage from the stomach. Of 91 cases with a small hernia, reported by Jones, 22 had a history of bleeding and, by the same author, 6 of 37 with large hernia had bleeding. Sahler reported 3 cases of bleeding out of 9 hernia found in his 100 consecutive gastro-intestinal Roentgen ray series. The Massachusetts General Hospital series of 221 cases, between 1930 and 1940, showed 12.6%, or 28 having a bleeding history. In our series of 41 cases, 8 had a positive history of hematemesis or melena which is 19.5% of the total group.

The second category is those series of cases which report anemia *per se* irrespec-

tive of the history of bleeding or blood loss. Some patients have hematemesis and do not show an anemia; some patients have hematemesis and anemia and some patients have an anemia and no symptoms of blood loss. A group of the same investigators who were shown in the above grouping are again listed as reporting the incidence of anemia. Though some of the series of cases were the same, the incidence of anemia here is different than the incidence of bleeding listed above. Ernstene,<sup>5</sup>

TABLE 2.—ANEMIA IN DIAPHRAGMATIC HERNIA

Author	Total cases of hernia	No. having anemia	% having anemia
Harrington . . . . .	60	7	11.7
Ernstene and McGurl . . . . .	59	2	3.4
Levy and Dugan . . . . .	26	1	3.9
Gilbert, Dey and Rall . . . . .	48	3	6.3
Held and Goldbloom . . . . .	13	4	30.8
Murphy . . . . .	67	47	66.7
Mass. Gen. Hosp. . . . .	221	27	12.2
I. U. Med. Center . . . . .	41	11	26.8

in 1940, reviewed 59 cases of esophageal hiatus hernia and found 2 with hypochromic anemia. Levy and Duggan,<sup>13</sup> observing 26 cases, found only 1 with anemia. W. P. Murphy,<sup>14</sup> in 1942, reported a series of 67 cases, each with a blood examination; 7 cases showed a macrocytic type of anemia and 40 showed a secondary anemia, which gave 66% of his cases with a hemoglobin of less than 12 gm. or a red blood count of under 4 million. In Harrington's 60 operated cases between 1925 and 1933, 7 (11.7%) had anemia. Gilbert, Dey and Rall<sup>8</sup> had an anemia in 3 of their 48 cases, and Held and Goldbloom<sup>12</sup> showed an anemia in 4 of their 13 cases. The report of the Massachusetts General Hospital in its series of 221 cases was surveyed and 27 of that group had an anemia. In our own series there were 11 patients who had an anemia and 30 who had a normal blood count, which gave an incidence of anemia of 26.8%.

In attempting to evaluate the anemia in diaphragmatic hernia in our series of 41 cases, we first had to set a standard which could be called a normal blood count for the locale from which this group of patients had come. It was found that males with a hemoglobin above 12 gm

and a red blood count of over 4 million would have to be considered normal. For the females, a hemoglobin above 11 gm. and a red blood count above 3.5 million was considered normal. From this standard we evaluated the state of the blood in our cases and found that 30 of the patients had a normal blood count and/or hemoglobin. The 11 cases which showed an anemia were all secondary anemias, some a normochromic and some a hypochromic type. There was no evidence of a macrocytic type in any of the patients who had anemia.

few to make at about treatment. was found that surgical repair t It is still present 2 postoperative c In those cases t mia improved i still present in temesis. The another patient is reported th matic hernia therapy.<sup>18</sup>

TABLE 3.—SUMMARY OF CASES OF ANEMIA

Case	Sex	Age	History of bleeding	Roentgen ray findings	Hgb. (gm.)	RBC
xL 36255	F	49	Pos.	Much of cardia stom.	9.5	3.00
xL 9308	F	74	Neg.	Large hiatus hernia	10.5	2.96
xL 64414	F	59	Neg.	Small esoph. hiatus hernia	10.5	3.20
xL 91661	F	57	Pos.	Thoracic stom. on r.	7.5	2.82
xL 95908	M	54	Pos.	Small diaph. hernia	11.0	3.43
xR 81550	F	7	Neg.	½ stomach in r. chest	10.5	..
xL 103953	M	60	Pos.	Large diaph. hernia of cardia	10.0	3.08
xL 74242	M	67	Neg.	Large diaph. hernia of cardia	9.5	2.87
xL 65359	F	59	Neg.	Obst. antrum stom. bowel in l. thorax	9.0	3.93
xR 88891	M	2	Neg.	Herniation on absence of l. leaf diaphragm	11.0	..
xL 65702	F	48	Neg.	Stom., colon, spleen, intest.	9.5	3.00

In the 11 cases which showed an anemia, 7 were females and 4 were males. Four of the patients had a positive history of hematemesis or melena and these were equally divided between males and females. The other 7 had had no recorded history of any gastro-intestinal hemorrhage or bleeding. There was no correlation between the hernial contents or the size of the hernia and whether the patients were anemic; there were equally as many small and large herniae in the normal group as among the 11 patients who presented the anemia.

Though the 11 cases of anemia are too

**Summary.** A review of the clinical entity diaphragmatic hernia, and the secondary anemia which may be found with it, has been presented. Forty-one more cases of hiatus hernia are listed. In this series 11 patients showed a secondary anemia, a percentage of 26.8. This incidence of anemia is not as high as some reported series, but is higher than a number of other series. It tends to substantiate the fact that anemia in diaphragmatic hernia is often found as part of the disease and that it does not have to be associated with a history of gastro-intestinal bleeding.



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# PROLONGED INCUBATION PERIOD AS AN EPIDEMIOLOGIC PRINCIPLE INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM JAUNDICE

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IN clinical medicine "the case" begins with the onset of sickness and terminates when the patient is well again; in epidemiology "the case" begins when the patient receives the infectious agent and lasts as long as he is infectious. In certain diseases the clinical and epidemiologic cases may closely coincide but in many they are widely or even totally divergent. In some diseases the epidemiologic case begins long before and long outlasts the clinical case and in others the majority of infected and infectious individuals never have any sickness at all—subclinical infection or healthy carriage.<sup>8</sup> Incubation periods have been judged from intervals of time between adjacent cases or have been established from repeated observation of definite intervals elapsing between exposure to known sources of infection and the onset of disease. In many instances, they have been more precisely determined by deliberate or experimental inoculation with the disease agent. In general, incubation periods have been interpreted as representing the interval between exposure to infection and onset of disease. For example, from an earlier study of the intervals between multiple cases in families, it was concluded that in poliomyelitis "the search for the source of the infection should be centered at about the 14th day before the onset of acute symptoms."<sup>3</sup> It subsequently became clear that this conclusion should be amended when it was found that the incubation period—and disease—was not always initiated at the time of exposure to the infectious agent but at times by some predisposing event having an effect on the host which initiated the infectious process in an individual

already harboring the virus.<sup>6</sup> More precisely, it may be said that "predisposing causes" may convert healthy carriage into incubation. A clear example is seen in bulbar poliomyelitis following tonsillectomy. In meningitis there are many indications that incubation may be most often initiated by some "predisposing" factor in persons already carrying the organism.

The mechanism involved in incubation periods is not known and since there are no signs or symptoms, it lends itself poorly to study. Yet, in some diseases its time factor is very precisely defined, in others this may vary within wide limits, and in some it may be definitely altered by certain special circumstances, as, for example, the prolonged incubation period under the protective influence of immune serum or other influences which "prepare" the host in the direction of resistance to inoculation with virus.<sup>2</sup>

PROLONGATION OF INCUBATION PERIODS. Sternberg and Reed<sup>37</sup> reported an early and interesting example of prolonged incubation period. From experiments on the protective effect of vaccinia immune serum against vaccination in monkeys, they concluded that the appearance of lesions is retarded as long as "there is present in the system of the vaccinated animal certain antitoxic substances contained in the serum, and that when these substances have been eliminated from the body, the process proceeds to a successful though somewhat modified course of development." Their protocols indicate that there was a retardation in appearance of the vaccinia reaction of about the same order as that in the other examples of prolongation of incubation period to be cited.

In the conduct of neutralization tests in poliomyelitis it has been observed that animals inoculated with mixtures of virus and non-immune serum develop the experimental disease—as do animals inoculated with virus alone—after an incubation period not exceeding 14 days. Inoculation with immune serum-virus mixtures usually affords complete protection. Exceptionally the disease develops after longer incubation periods (Aycock and Luther).<sup>7</sup> In the course of a study of various factors involved in the neutralization test, Schaffer and Muckenfuss<sup>35</sup> reported data on the incubation periods in a large number of tests done with a single strain of poliomyelitis virus and the same pool of human convalescent serum. The average incubation period following inoculation with virus and non-immune serum was 8.3 days and with virus-immune serum 14.3 days—a prolongation of 72% (Chart 1).

Sullivan in the laboratory of the John F. Enders\* have kindly been made available. In titrations, usually in dilutions of  $\frac{1}{100}$  to  $\frac{1}{800}$  of  $\gamma$ -globulin, average survival time of mice injected with dilutions of  $\frac{1}{800}$  of globulin (81.9% succumbing), was 6.2 days, and with  $\frac{1}{100}$  dilutions (with only 4.5% succumbing), 8.7 days. Thus the prolongation of incubation period as a result of the protection of  $\gamma$ -globulin was (within the range tested) 42% (Table 1).

Duncan, Christian, Stokes, Rexer, Nicholson and Edgar<sup>14</sup> have observed prolongation of the incubation period by the administration of  $\gamma$ -globulin to patients already in the incubation period of homologous serum jaundice. Their data comprise 52 out of 4780 battle casualty patients (with no history of jaundice) who had received blood or plasma or both at the time of injury and who developed hepatitis within 5 months, but after

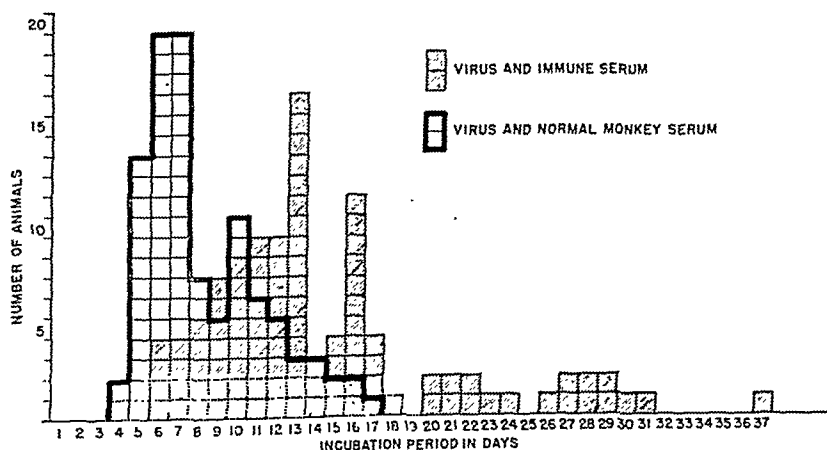


CHART 1.—Poliomyelitis. Neutralization tests showing incubation periods in animals inoculated with mixtures of virus and immune serum and mixtures of virus and normal monkey serum. Average prolongation with immune serum—8.3 days (72%).<sup>35</sup>

Data relating to the average survival time (incubation period in the sense that death of the inoculated animal is the "uniformly recognizable sign of the disease") in mice employed in neutralization tests with normal human  $\gamma$ -globulin and influenza A virus PR 8, by Miss Julia

10 days from the date of administration of  $\gamma$ -globulin. Of these patients 2406 received  $\gamma$ -globulin; 29 developed hepatitis, the mean interval from the original transfusion to the development of hepatitis being 103 days, and from administration of  $\gamma$ -globulin, 53 days. Of the 2374 alternate

\* These studies were carried out by Dr. John F. Enders of the Department of Bacteriology of the Harvard Medical School, with  $\gamma$ -globulin prepared by the Department of Physical Chemistry, Harvard Medical School, from blood collected by the American Red Cross, under a contract recommended by the Committee on Medical Research and Development and Harvard University.

patients used as controls, 23 developed hepatitis after a mean interval of 84 days from original transfusion and 34 days from the day on which they were paired with patients receiving  $\gamma$ -globulin and designated as controls. (The average intervals between the time the 2 groups received blood or plasma and the time they were injected with globulin or designated as controls, were "almost identical.")

guishable—in clinical manifestations, severity, or mortality—from that following shorter incubation periods. This would indicate that the action of the immune serum is restricted to prevention of disease entirely or to prolongation of incubation. This is true in experimental poliomyelitis, apparently so in the  $\gamma$ -globulin influenza tests, as well as in homologous serum jaundice where  $\gamma$ -globulin was

TABLE 1.—PROLONGATION OF INCUBATION PERIOD—IMMUNOLOGIC PROTECTION: NORMAL  $\gamma$ -GLOBULIN AGAINST INFLUENZA A VIRUS PR 8

Globulin dilution	Mice surviving	Mice dying	% dying	Av. days survival in mice dying
1-800 . . . . .	58	260	81.9	6.2
1-400 . . . . .	80	232	74.3	7.1
1-200 . . . . .	203	111	35.3	7.7
1-100 . . . . .	298	14	4.5	8.7

Thus, as concluded by these authors, the administration of a single dose of 10 cc. of  $\gamma$ -globulin (on the average on the 50th day of an average incubation period in untreated controls of 84 days) retarded the onset of the acute phase of hepatitis by an average period of 19 days (23%). However, since  $\gamma$ -globulin was administered late in the incubation period, a more exact expression of the effect of  $\gamma$ -globulin would be the degree of prolongation of that part of the incubation period represented by the interval between the date of administration of globulin and onset of the disease in controls—a prolonged "incubation" of 55% over that of the controls.<sup>14</sup>

Prolongation of incubation periods does not appear to be a simple "coating of virus with antibody," whereby the onset of symptoms is delayed for a constant period. Prolongation by immune serum is more nearly proportionate to the length of the incubation periods of the several diseases, or (in the case of homologous serum jaundice treated in mid-incubation period with  $\gamma$ -globulin) to that part of the incubation affected by immune serum. Thus, actual prolongations of 6, 2.5 and 19 days in the 3 examples cited represent degrees of prolongation of 72%, 42% and 55%. The disease ensuing after a prolonged incubation is in no way distin-

administered in the incubation period of the disease. In other words, prolonged incubation period is the only effect produced on disease resulting from inoculation of virus "partly neutralized" by immune serum. In this connection a comparison with modification of measles with immune serum would be of interest.

INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM JAUNDICE. The striking difference between infectious hepatitis and homologous serum jaundice (in jaundice occurring spontaneously and following injection of human serum), and the main basis for the question of there being 2 separate entities, is the difference in incubation periods—striking in terms of time alone—but in proportion to the length of the incubation period, not greatly in excess of the prolongation of incubation periods obtained in other diseases when virus is "partially neutralized" with immune serum. There are epidemiologic grounds for the assumption that icterogenic serum is derived from persons either in the incubation, acute or convalescent stage of infectious hepatitis or from persons subclinically infected with it. On the other hand, there are good epidemiologic grounds for assuming that the virus causing homologous serum jaundice is not a different etiologic agent from that causing infectious hepatitis. For instance, there is no evidence for the

existence of a spontaneous disease caused by a homologous serum jaundice virus which could serve as the "virus reservoir" for homologous serum jaundice. Actually, it would seem to be somewhat of an anomaly to say that many persons harbor such a virus without its ever causing disease in them and yet, when their blood serum is injected into others, the disease is readily produced. It would appear much more logical to infer that the "virus reservoir" for homologous serum jaundice is individuals who harbor the virus of infectious hepatitis—one evidence of which is the occurrence of the spontaneous disease in them, and another that blood serum from them produce a disease indistinguishable from homologous serum jaundice when inoculated into others—even as to incubation period.

In this paper, the possible relationship of prolonged incubation resulting from inoculation of virus in the presence of immune serum to the epidemiology of infectious hepatitis and homologous serum jaundice will be discussed.

The question is raised whether the shorter incubation in infectious hepatitis and the longer incubation in homologous serum jaundice may not be the result of infection, on the one hand by virus free of admixture with serum, and on the other hand, by the same virus partially neutralized by admixture with serum of donor, recipient, or both. To shed some light on this question, data have been collected from the literature on both infectious hepatitis and homologous serum jaundice where incubation periods are given in cases following inoculation (or infection) under circumstances which imply either serum-virus mixtures or serum-free virus.

The first category comprises cases of both infectious hepatitis and homologous serum jaundice known to have been transmitted by virus supposedly free of admixture with serum; and the second, cases of both diseases in which transmission was accomplished with parenteral injection of serum in which virus was present. Among the former are experimental transmissions

of each disease to volunteers by intranasal or oral administration of nasal washings or feces, and cases contracted from cases of the same disease by direct contact. The latter comprise only cases of both diseases from whom the disease was transmitted to others by parenteral injection of blood or serum. Cases of homologous serum jaundice in the usual sense—contracted following inoculation of serum or plasma from supposedly normal individuals (or of unknown origin)—are not included.

For comparison of the different categories of cases from the point of view of prolongation of incubation periods, the data are restricted to instances where the type of disease from which the infectious agent was obtained, the manner by which it was transmitted, and incubation periods, were known. This requirement limits many of the observations used to transmission experiments and, because of the fact that only human volunteers can be used, these are not numerous. <sup>9-13,16-18,20,22,23,25-34,38,39</sup> Even though the numbers are small, however, there is a consistency in the results of the comparisons which suggests that the findings are valid.

Of 82 cases of infectious hepatitis, in 60 the disease is known to have been transmitted intranasally, orally, or by contact, with an average incubation period of 28.4 days; while in 22 cases in which transmission was by the parenteral injection of serum from other cases of infectious hepatitis, the average incubation period was 61.6 days—a prolongation of 116%. Of 17 cases of homologous serum jaundice, in 10 transmission was by intranasal or oral administration of material from cases diagnosed as homologous serum jaundice, with an average incubation period of 46.1 days; while in 7 cases following parenteral injection, it was 87.8 days—a prolongation of 90.4%. (Incubation periods by weeks are shown in Chart 2.) It may be stated that in 3 of the cases of homologous serum jaundice used here, transmission occurred by contact under circumstances where the presence of infectious hepatitis could be satisfactorily ruled out.

The incubation periods of 38, 43 and 49 days are the longest possible incubation periods, but the circumstances are such that they all might have been shorter. In both infectious hepatitis and homologous serum jaundice where transmission was accomplished by intranasal, oral or contact infection, the incubation periods tended to be that which is generally recognized as that of infectious hepatitis. When either disease was transmitted by parenteral injection of serum from the same type of case, the incubation period

eases. Prolonged incubation period resulting from admixture of virus with serum containing antibodies is suggested as a probable explanation for the longer incubation period in homologous serum jaundice.\* The degree of prolongation of incubation period, as between infectious hepatitis and homologous serum jaundice, is greater than that observed in any of the other examples of prolonged incubation periods induced by admixture of virus with immune serum. In all these, however, prolongation was induced either by

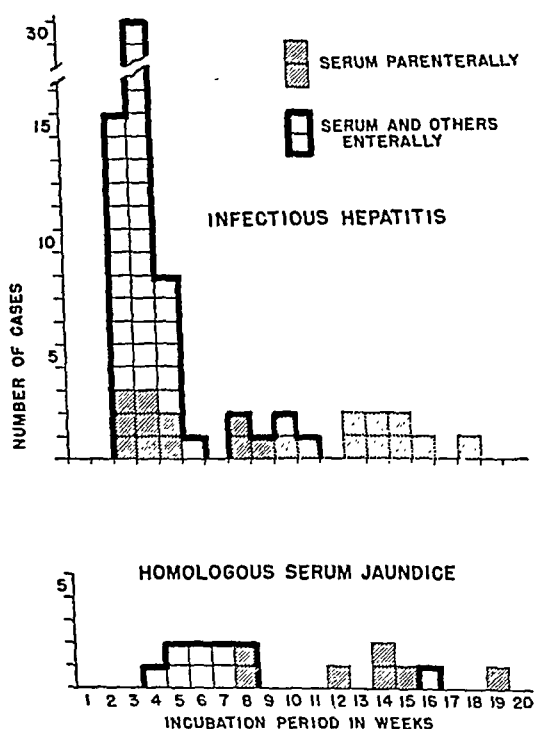


CHART 2.—Infectious hepatitis and homologous serum jaundice. Incubation periods following inoculation of serum and other virus containing material enterally, and inoculation of serum containing virus parenterally. Prolongation incubation periods with parenteral serum of 116% and 90.4%.

was that which is regarded as characteristic of homologous serum jaundice (following injection of supposedly normal serum).

It thus appears that the difference in the incubation periods of infectious hepatitis and homologous serum jaundice might be accounted for largely by differences in the manner of transmission of the 2 dis-

*in vitro* mixture of virus and serum or injection of virus into hosts protected by immune serum. That prolongation in incubation period may be additive depending in part on antibodies at the source of virus (in the serum of the donor patient), admixture *in vitro* (inclusion of immune serum in pools) or antibodies in the recipient host, is suggested by the observation

\* In most of the reports from which data have been collected, there is not sufficient information to make a precise analysis of the possibility that "prolongation of incubation periods" may be the result of retarded recognition resulting from modification of the disease from serum. Study of the various reports, however, does not give any indication that the thresholds of recognition of the 2 types of cases are different.

cited that when individuals in the already prolonged incubation period of homologous serum jaundice are injected with  $\gamma$ -globulin, the incubation period is still further prolonged. Fox<sup>19</sup> observed wide variation in the frequency of icterus following yellow fever vaccination, with known icterogenic lots of the vaccine in

hepatitis and homologous serum jaundice combined, where the virus used was obtained from nasal washings or feces, or where the disease was naturally transmitted by contact, intranasal or oral inoculation of serum-free virus, the average incubation period was 29.9 days. In 8 cases where blood serum from the donor

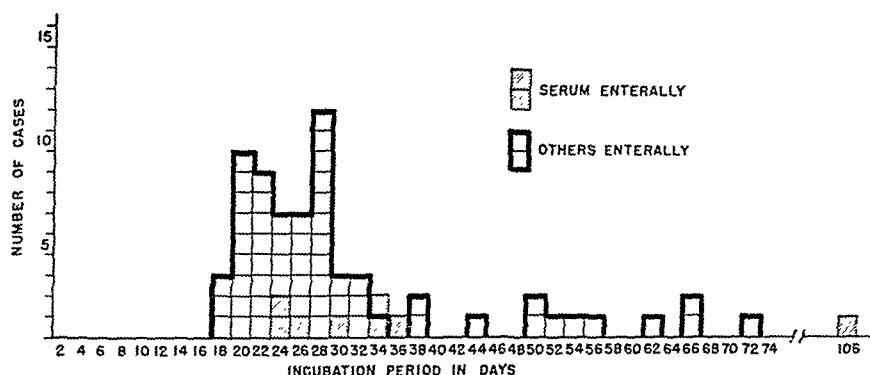


CHART 3.—Homologous serum jaundice and infectious hepatitis. Incubation periods intranasal or oral inoculation with serum-free virus as compared with intranasal or oral inoculation of serum containing virus. Prolongation with serum containing virus of 29.7%.

TABLE 2.—INCUBATION PERIODS IN NEUTRALIZATION TESTS AND IN CERTAIN CATEGORIES OF CASES OF INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM JAUNDICE—SHOWING DEGREE OF PROLONGATION ASSOCIATED WITH SERUM

Materials used	Average days incubation period	% prolongation
<b>Poliomyelitis:</b>		
Normal monkey serum . . . . .	8.3	
Human convalescent . . . . .	14.3	72.2
<b>Influenza:</b>		
$\frac{1}{100}$ $\gamma$ -globulin . . . . .	6.2	
$\frac{1}{100}$ $\gamma$ -globulin . . . . .	8.7	40.3
<b>Homologous serum jaundice:</b>		
Controls . . . . .	34.1	
$\gamma$ -globulin . . . . .	52.8	54.8
<b>Infectious hepatitis:</b>		
Nasal washings, feces, or serum—enterally . . . . .	28.4	
Serum—parenterally . . . . .	61.6	116.9
<b>Homologous serum jaundice:</b>		
Nasal washings, feces, or serum—enterally . . . . .	46.1	
Serum—parenterally . . . . .	87.8	90.4
<b>Infectious hepatitis and homologous serum jaundice:</b>		
Nasal washings or feces—enterally . . . . .	29.9	
Serum—enterally . . . . .	38.8	29.7

similarly vaccinated localities, and in households within these localities. One possible explanation for this was preëxisting immunity to the icterogenic agent contained in the vaccine, presumably resulting from previous infection with infectious hepatitis. In this connection, it is of interest that in 62 cases of infectious

patient was employed for intranasal or oral administration, the average incubation period was 38.8 days—a prolongation of 29.7% (Chart 3). There would, therefore, seem to be a possibility that admixture of serum from the donor patient (presumably containing antibodies) might account in part for the prolongation of

incubation periods in homologous serum jaundice over that of infectious hepatitis.

Comparisons of incubation periods with the degree of prolongation in all the different categories used in this study are summarized in Table 2. It may be of some interest to note here that when known non-immune animals were injected with supposedly serum-free virus mixed with known immune serum (poliomyelitis neutralization), the degree of prolongation was 72%. In infectious hepatitis and homologous serum jaundice, the degree of prolongation in cases where the virus was

persons), there may be no admixture of virus with antibodies in either.

The question of there being separate etiologic agents, apparently raised in the first place on the basis of the difference in incubation periods, had led to studies looking for other differences. Some are contradictory; others are based on small series of observations, and in still others the conclusion that there are 2 etiologic agents appears to be a matter of interpretation.

The chief differences in the 2 types of jaundice which have been emphasized,

Poliomyelitis Neutralization Tests:

Virus and non-immune serum in vitro

Virus and immune serum

72%

Infectious hepatitis:

No serum

Experimental transmission:

Virus and serum of donor

29%

Homologous serum jaundice in general

29%

72%

101% prolongation over  
infectious hepatitis

Length of incubation period (with prolongations in percentages).

CHART 4.—Theoretical explanation of prolongation of incubation period of homologous serum jaundice over infectious hepatitis.

contained in serum from the donor was 29.7% more than in cases where the source of virus was presumably serum free (nasal washings or feces). If these 2 prolongations, namely, in poliomyelitis neutralization (72%) and virus hepatitis (29%), are added, they closely approach the prolongation of incubation period in homologous serum jaundice, in general, over that of infectious hepatitis (101%) (Chart 4). This would suggest that there may be antibodies both in the serum of the donor and recipient patients in homologous serum jaundice; while in naturally occurring infectious hepatitis (in non-immune

are differences in clinical manifestations, lack of cross-immunity, and the absence of contagiousness in homologous serum jaundice. The voluminous literature on these 3 points will not be reviewed here, but it may be pointed out that the weight of opinion seems to be that the 2 types of jaundice are clinically and pathologically identical. The observation of such manifestations as arthritis and skin rashes, reported as characteristic of homologous serum jaundice, has likewise been reported in infectious hepatitis; and, in general, it may be said that no clinical manifestations as yet have been established as pathog-



nomonic of either of the 2 types of jaundice.<sup>21,24</sup>

Knowledge of immunity in the 2 types of icterus is extremely limited because of the fact that observations have been confined to human studies. We believe that there is not yet sufficient information to establish the 2 diseases as being due to immunologically distinct agents. Too few immunologic studies have been done to rule out the possibility that lack of cross-immunity may be due to different strains of the same virus which will produce either infectious hepatitis or homologous serum jaundice. The possibility that the same lack of cross-immunity may be encountered in different outbreaks of either disease has not been excluded. It may be pointed out that cross-immunity, as has been discussed in a previous paper in relation to bacteria,<sup>4</sup> while serving to distinguish particular strains of the same organism, is not necessarily a criterion for etiologic specificity.

Many authors have stressed as a difference between the 2 diseases that homologous serum jaundice does not give rise to naturally occurring secondary cases. There is some question as to whether this point has yet been adequately studied. As has already been stated, "the search for the source of infection should be centered at a time preceding onset of symptoms by the length of the incubation period." With the existing conviction as to a difference in the incubation periods of the 2 types of hepatitis, it is not unlikely that secondary cases of homologous serum jaundice would be sought for at a longer interval and that cases actually occurring after a shorter interval following exposure to previous cases might well have been designated as infectious hepatitis and assigned, not to a relatively recent exposure to other cases of homologous serum jaundice, but to some supposed exposure to infectious hepatitis. It is true that relatively few cases of long incubation period infectious hepatitis and short incubation period homologous serum jaundice have been recorded. This might be ac-

counted for in part by the use of incubation periods as the basis of differential diagnosis in many cases of otherwise indistinguishable jaundice. Finally, it is possible that there may be an actual difference in contagiousness. In infectious hepatitis, the infectious agent entering through the mouth or nose might be contagious for example, throughout its incubation period; while in homologous serum jaundice, the virus, due to the manner of inoculation, might not appear on external surfaces of the body until later or not at all.

Findlay and MacCallum,<sup>15</sup> in 1938, had suggested that jaundice following yellow fever vaccination was caused by virus in serum (used in preparation of the vaccine) obtained from apparently healthy persons who were in reality suffering from subclinical or very mild infectious hepatitis. Shank and Mirick<sup>36</sup> have observed an outbreak of icterus which is in support of this early opinion and at the same time well illustrates all the epidemiologic points presented in this paper. Following the injection of some 750 individuals with diluted human plasma, 267 cases of jaundice occurred. The average interval between the injection of plasma and the development of symptoms was about 70 days. In an equal number of persons working in the same establishment who did not receive plasma, 14 verified and probably 8 other cases of spontaneous jaundice occurred late in the outbreak. The average interval between the date of inoculation of plasma and the development of jaundice in the uninoculated or "control" group was about 100 days. No cases of spontaneous jaundice had occurred in the group during the preceding 3 years. Thus, the average interval between the primary cases (following inoculation with plasma) and the secondary cases in the uninoculated group was about 30 days—a period coinciding with the incubation period of infectious hepatitis.

In institutional outbreaks of measles and German measles previously reported,<sup>1,5</sup> in each within a period of 8 weeks the primary case and 4 secondary waves of

measles occurred and in German measles the primary case and 2 secondary waves occurred. The average interval between waves in measles was 11.2 days and between waves in the German measles outbreak, 18.6 days. In these 2 frequently confused diseases the intervals between waves of cases in institutional outbreaks are a distinguishing feature.

It would therefore appear, by analogy somewhat in reverse, that in the outbreak of jaundice observed by Shank and Mirick the cases in the secondary wave (spontaneously occurring jaundice) correspond to the usual definition of infectious hepatitis. But since the source of infection for this wave of cases apparently was a preceding wave of cases of homologous serum jaundice, it is indicated that the long incubation period resulted from parenteral injection of serum and the short incubation from spontaneous infection presumably with serum-free virus by contact.

**Summary and Conclusions.** In neutralization and protection tests in a number of virus infections having different incubation periods, a portion of the animals inoculated with mixtures of virus and immune serum develop the disease following incubation periods that are longer than those resulting from inoculation with virus and non-immune serum. Prolongation is proportionate to the length of the incubation periods of each of the several diseases. The degree of prolongation of the incubation period of homologous serum jaundice over that of infectious hepatitis is of the order of that observed in other neutralization or protection tests.

In the light of this epidemiologic principle, it is suggested that the difference in the incubation periods of infectious hepatitis and homologous serum jaundice is due to differences in the manner of transmission of a single virus which involve admixture of virus with antibodies.

The shorter incubation period, generally regarded as characteristic of infectious hepatitis, occurs when transmission of either of the 2 types of jaundice is accomplished by intranasal or oral administration, or by contact (serum-free virus). The longer incubation period, regarded as characteristic of homologous serum jaundice, follows the transmission of either of the types of jaundice by the injection of serum containing virus. It is postulated that the prolongation of the incubation period of homologous serum jaundice over that of infectious hepatitis is the result of partial neutralization of the virus by admixture with serum containing antibodies of either the donor or recipient patient or by the *in vitro* action of serum containing antibodies on the virus.

The establishment of naturally occurring infectious hepatitis as the "virus reservoir" for homologous serum jaundice would serve to emphasize the extent of this "reservoir" and the importance of the study of methods for insuring sterility. This leads to the suggestion that, until a method of insuring sterility is found, in the administration of serum-containing products these dangers are always present; consequently the indications for their use must be important.

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# CARONAMIDE, A COMPOUND THAT INHIBITS PENICILLIN EXCRETION BY THE RENAL TUBULES, APPLIED TO THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS\*

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A NEW compound, caronamide,<sup>26†</sup> has been described as orally effective to elevate the plasma concentrations of penicillin. Large losses of penicillin in the urine are known to occur, and since it is now established that approximately 80% of the loss is through the renal tubules,<sup>9,21</sup> an agent capable of inhibiting the tubular excretion of penicillin might be expected to enhance the levels of penicillin in the plasma. These effects have been observed to follow the administration of diodrast,<sup>22</sup> para-aminohippuric acid<sup>4,7,9</sup> and benzoic acid.<sup>12,25</sup> Diodrast and para-aminohippuric acid have been employed in the treatment of subacute bacterial endocarditis,<sup>1,18,20,24</sup> but the necessity of administering large amounts of either substance by constant intravenous infusion has limited their usefulness.

It has been hypothesized that the physiologic and reversible inhibition of the penicillin transport mechanism is due to a "substrate competition between penicillin which is excreted by the tubules, and 4'-carboxy-phenylmethanesulfonanilide, which is essentially refractory to excretion by the transport mechanism."<sup>2</sup>

In preliminary clinical investigations,<sup>15</sup>

penicillin plasma concentrations were enhanced from 3 to 7 fold by the oral administration of caronamide, and no serious toxic manifestations were observed. Accordingly, we felt justified in applying caronamide to the treatment of a patient with subacute bacterial endocarditis due to a strain of *Streptococcus viridans* resistant to penicillin and to streptomycin.

**Case Abstract.** The patient, M. C., was a white female aged 51 years. The diagnosis of subacute bacterial endocarditis was established on Aug. 1, 1946, at which time the blood culture was positive and the heart murmurs were observed to have changed in character.

As shown in Table 1, the patient had received 4 courses of antibiotic therapy, 2 of penicillin and 2 of streptomycin prior to this study. The first course totalling 14,400,000 units of penicillin was given over a period of 29 days administered by intramuscular injection every 3 hours in a daily dose of 540,000 units. Following this course of therapy, the blood culture became negative but signs of relapse were observed on October 14, and blood cultures remained positive until the second course of penicillin therapy began on October 29. A daily dose of 750, 000 units of penicillin was given for

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The penicillin used in this investigation was supplied through the courtesy of Charles Pfizer & Co., Inc. Caronamide was supplied through the courtesy of Sharp & Dohme, Inc.

† Since we have had the benefit of knowing by personal communication about many of the investigations on caronamide that are now in progress, the Bibliography contains a number of references to unpublished data.

50 days, the total amount being 37,500,000 units. Penicillin was administered by intramuscular injection every 2 hours. Again the blood cultures became negative and the disease appeared to be in remission but renewed activity of the disease and a positive blood culture appeared on Dec. 31, 1946. The original sensitivity of the strain of *Streptococcus viridans* was 0.03 unit of penicillin per cc., but under therapy this decreased to 0.5 unit per cc. Accordingly, a change to streptomycin was made on January 13. A daily dose of 3 gm. was given by intermittent intramuscular injections every 4 hours. Treatment was continued for 15 days and a total of 45 gm. of streptomycin was administered. When streptomycin therapy was initiated, the organism was sensitive to 0.5 unit per cc. but after treatment 5 units

mide as an adjunct to intensive penicillin therapy. In Chart 1 the details of this patient's fifth course of antibiotic therapy are presented. The record of rectal temperatures suggests the severity of the illness under treatment; weight loss, anorexia and asthenia paralleled the febrile course. During this course a daily dose of 4,000,000 units of penicillin was chosen arbitrarily and administered intramuscularly in divided doses of 500,000 units dissolved in 2 cc. of sterile saline. Treatment was continued for 28 days. During this time repeated dose response curves were defined following individual injections of 500,000 units of penicillin. An effort was made to determine the curve at

TABLE 1.—SENSITIVITY TESTS ON M. C.

W 51— <i>Rheum. Ht. Dis. and Subac. Bact. Endoc. (Strep. viridans)</i>					
Dates	Blood cultures	Yellow	Penicillin G	X	Streptomycin
1946					
Aug. 1	Pos.	..	No tests		
		<i>Course I—14,400,000 u. of Penicillin</i>			
Oct. 26	Pos.	0.03 u./cc.			
		<i>Course II—87,500,000 u. of Penicillin</i>			
Dec. 31	Pos.	0.50 u./cc.			
1947					
Jan. 2	Pos.	0.50 u./cc.	..	..	0.5 u./cc.
		<i>Course III—45 Gm. of Streptomycin</i>			
Feb. 1	Pos.	1.00 u./cc.	1.0 u./cc.	..	5.0 u./cc.
		<i>Course IV—24 Gm. of Streptomycin</i>			
Feb. 10	Pos.	0.50 u./cc.	0.5 u./cc.	0.5 u./cc.	10,000 u./cc.

per cc. were needed to inhibit growth. A second course of 24 gm. of streptomycin was given over a period of 8 days. At the conclusion of the fourth course of treatment and the second course of streptomycin, the organism was found to have increased its resistance to streptomycin by 20,000 fold, 10,000 units per cc. being required to inhibit growth and the organism was resistant to 0.5 unit per cc. of amorphous penicillin and fraction G and X. After 4 courses of treatment the blood cultures remained positive and the bacterial endocarditis was active as indicated by fever, embolic phenomena and a deterioration of the general state of health.

Since the resistance of the infecting organism in this instance appeared to require high penicillin plasma concentrations, it seemed justifiable to use carona-

the same time of day (between 9 A.M. and 12 NOON) in order that the relationship to meals, fluid intake and diurnal changes in temperature would be comparable. Caronamide was administered for 25 days, the daily dose varying from 12 to 24 gm. The drug was administered orally at 3 hourly intervals and penicillin was injected simultaneously.

Inasmuch as a pharmacologically active compound was being administered for the purpose of temporarily inhibiting a function of the renal tubules, an effort was made to determine whether or not there was any interference with renal function as indicated by the elimination of blood urea nitrogen, creatinine and uric acid. Weekly determinations during the 30 day

period of observations showed no change in the values of these substances in the blood (Chart 1).

The skin rash which appeared on the 16th day of therapy was a generalized, morbilliform rash of the type commonly seen in association with drug sensitivity. Since we were employing a new, relatively untried compound, caronamide was immediately suspected of being the cause of this rash. Our dermatologic consultants, however, regarded it as similar to those commonly encountered during penicillin

excretion of "benadryl" were unavailing. The excitation of the patient apparently produced by the administration of "benadryl" led to the speculation that caronamide might be inhibiting the excretion of this compound.

On the 22nd day of continuous penicillin therapy, a sufficient supply of crystalline penicillin G became available and thereafter this type of penicillin was used exclusively. The skin rash faded despite continued treatment with penicillin and caronamide so that on the 28th day of

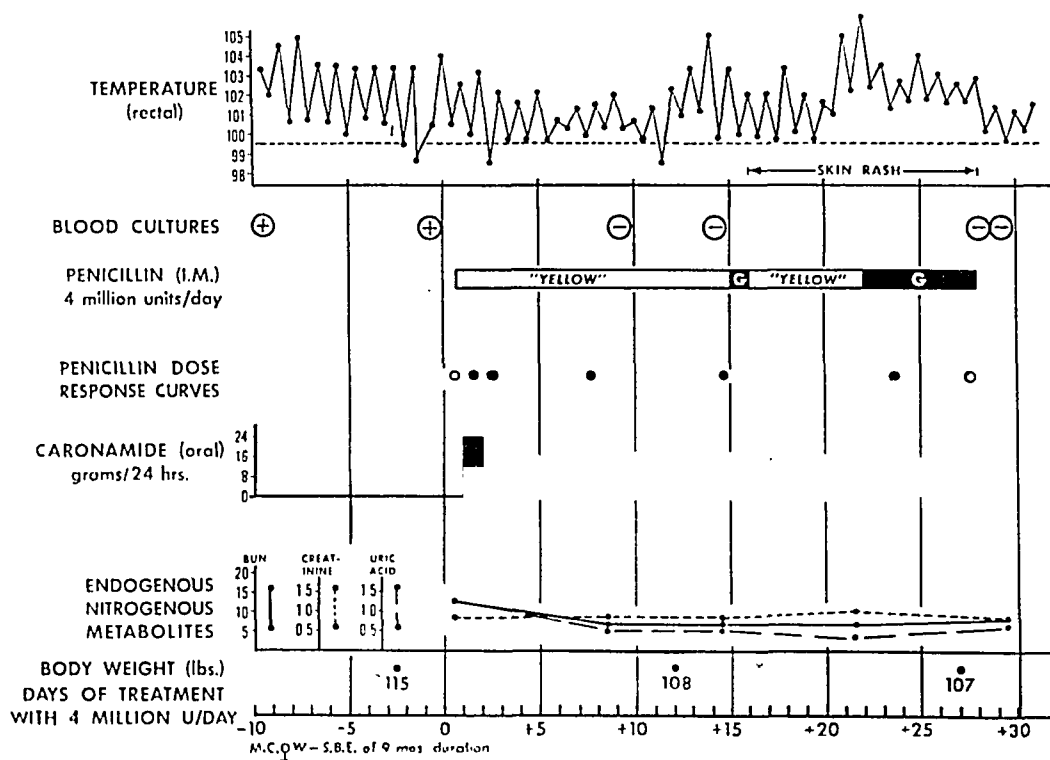


CHART 1.—Penicillin-caronamide antibiotic therapy (Course 5).

therapy. It was recommended that crystalline penicillin G be substituted for ordinary amorphous (yellow) penicillin. The supply of crystalline penicillin G on hand did not permit this change. Treatment with amorphous (yellow) penicillin and caronamide was continued, and "benadryl" was administered.

Contrary to common experience, "benadryl" appeared to cause excitation and was therefore discontinued. "Pyribenzamine" was better tolerated. Our efforts to learn something concerning the renal

treatment, the patient's skin was clear. Our reason for believing that this skin rash was due to an impurity present in the ordinary amorphous (yellow) penicillin will be referred to later. There seems to be little doubt that the secondary temperature rise reflected the appearance of drug sensitivity rather than reactivation of the bacterial endocarditis. On the 9th day of this course of treatment the blood cultures became negative and remained so.

The dose response curves indicated in Chart 1 are presented in detail in Chart 2.

Each dose response curve was defined following an intramuscular injection of 500,000 units of penicillin. Blood was withdrawn for assays 15 minutes, 30 minutes, 1, 2 and 3 hours after individual doses of penicillin. The precaronamide control curve began at 16.54 units of penicillin per cc. of plasma at 15 minutes, and at the end of 3 hours had declined to 2.71 units of penicillin per cc. Immediately after the definition of this curve, caronamide was administered orally 3 gm. every 3 hours until the following day at

is suggested that there was a carry-over effect from the previous day of treatment with 24 gm. of caronamide. The likelihood of this explanation is strengthened by the observation that after 12 gm. per day for 5 days, the dose response was little different from the precaronamide control curve. Since 12 gm. per day appeared to be ineffective, the dose of caronamide was increased to 16 gm. per day. After 4 days on this schedule, a dose response curve was defined, and it was found that the plasma concentrations had

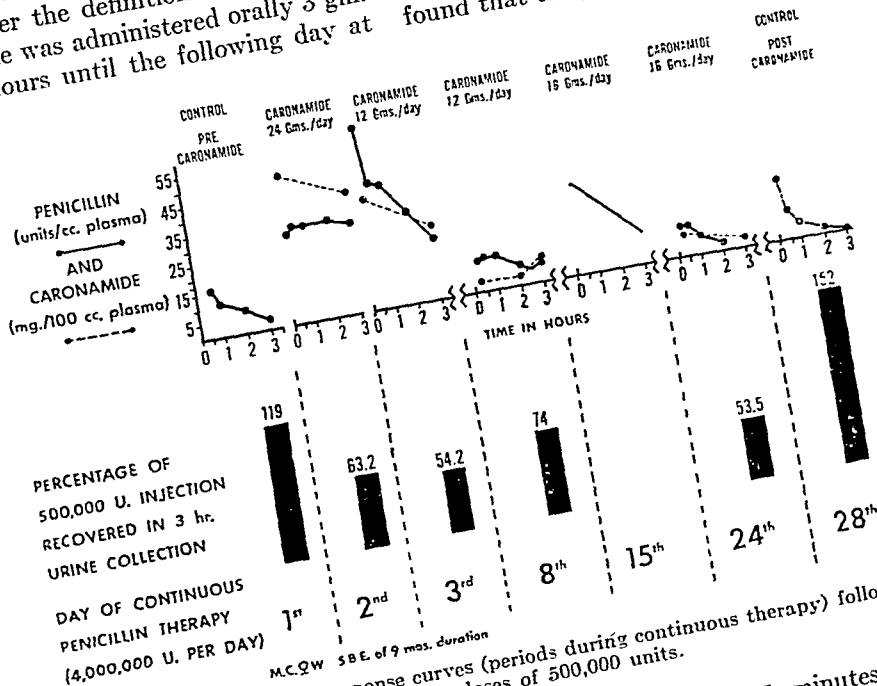


CHART 2.—Penicillin dose response curves (periods during continuous therapy) following intramuscular doses of 500,000 units.

which time the second dose response curve was determined. Throughout this entire 3 hour period, the penicillin plasma concentration was approximately 31 units of penicillin per cc. The dose of caronamide was reduced to 12 gm. per day and on the every 3 hours for 24 hours and on the 3rd day the curve showed the penicillin plasma concentrations were 62.59 units per cc. at 15 minutes and at the end of 3 hours had declined to only 20.67 units per cc. It is not entirely clear why, on 12 gm. of caronamide, the plasma concentrations of penicillin should have been higher than when 24 gm. were given. It

increased so that 15 minutes after an injection of penicillin the concentration was 31.46 units per cc. and at the end of 3 hours was still 15 units per cc. After 9 days, however, the dose response curve again was little different from the precaronamide control curve. Inasmuch as the patient's condition had improved, and several weeks, this course of therapy was terminated. Before doing so, however, a postcaronamide control curve was obtained. This second control curve begins at 20.89 units per cc. and declined during 3 hours to 1.99 units.

Quantitative urinary collections were made while the above curves were described and in both of the control periods more than 100% of the injected dose of penicillin was recovered in the urine. The urinary recoveries of penicillin during therapy with caronamide averaged 61%. It might be expected that, if caronamide blocks the excretion of penicillin by the renal tubules, the elevation of plasma concentration of penicillin might be reflected in a temporarily reduced amount of penicillin in the urine. The findings

ously and the correlation between the concentrations of caronamide in the plasma and the enhancing effect upon the plasma concentration of penicillin is apparent.

Although the patient showed no clinical or laboratory evidence of relapse, another course of antibiotic therapy was given to insure against reactivation of a possible latent infection. The sixth course of antibiotic therapy (Chart 3) began 1 week after the termination of Course V. One million units of penicillin were given daily for 25 days and crystalline penicillin G

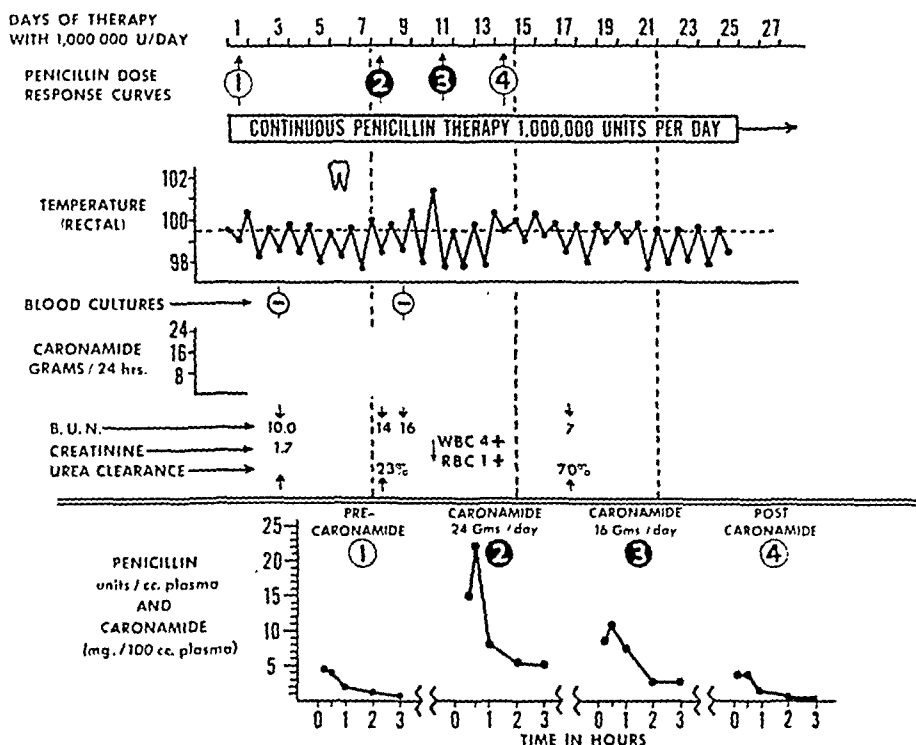


CHART 3.—Penicillin—caronamide antibiotic therapy (Course 6).

on the days when plasma levels of penicillin were increased and recoveries in the urine reduced are compatible with this expectation. On the other hand, on the 8th and 24th days (Chart 2) the recovery of penicillin in the urine was below the expected percentage, and at the same time the plasma concentrations of penicillin were not enhanced. At the present time we are unable to explain this apparent discrepancy.

Caronamide and penicillin plasma concentrations were determined simultane-

ously throughout. Intermittent intramuscular injections of 125,000 units were given every 3 hours. Caronamide in doses of 3 gm. every 3 hours was given for a period of 8 days. Thereafter, for an additional 4 days caronamide was given in a dose of 16 gm. per day, or 2 gm. every 3 hours. Despite the concomitant administration of penicillin G and caronamide, no skin rash appeared. For this reason we are inclined to feel that the skin rash previously noted was probably due to an

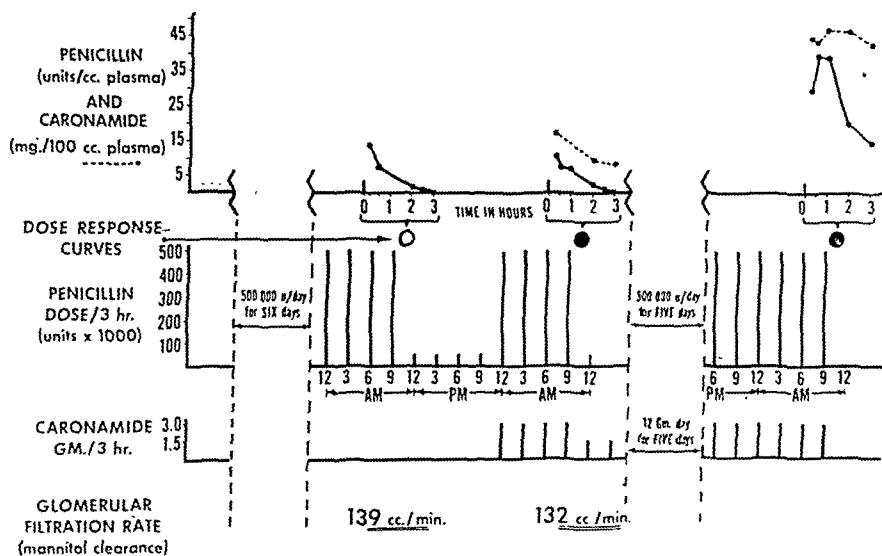


impurity in the amorphous (yellow) penicillin.

Following the 8 days of caronamide therapy at the level of 24 gm. per day the blood urea nitrogen rose slightly from its previous level; the urea clearance fell to 23% and cellular elements were present in the urine. Within 10 days after discontinuance of caronamide the blood urea nitrogen returned to the previous level of 7 mg. per 100 cc., the urea clearance rose to 70% and microscopic examination of the urine showed disappearance of both red and white blood cells. The rectal tem-

perature rose from 98.6° to 99.2° in 15 minutes, and at the end of 3 hours was still 5.42 units per cc. On a smaller dose of caronamide, 2 gm. every 3 hours, the plasma concentration of penicillin at the end of 15 minutes was 8.23 units per cc. and at the end of 3 hours was still 2.45 units per cc. The postcaronamide control curve compared favorably with the pre-caronamide curve; at 15 minutes the plasma concentration was 4.11 units per cc. and at 3 hours, 0.17 unit per cc.

Although the enhancing effect of caronamide upon the plasma concentrations of penicillin was not apparent in every dose



C. T. 116W Convalescent from Pneumonia

CHART 4.—Penicillin dose response curves following intramuscular doses of 500,000 units.

peratures during this course of antibiotic therapy were in sharp contrast to those during Course V, and this normal temperature record paralleled the patient's general improvement.

During Course VI both control and caronamide modified dose response curves were obtained as before. In the pre-caronamide control curve at 15 minutes the plasma concentration of penicillin was 4.19 units per cc. and at the end of 3 hours, only 0.25 unit per cc. When caronamide was administered in a dose of 3 gm. every 3 hours, the concentration of penicillin in the plasma was 14.77 units per cc. at

response curve, the results were sufficiently striking to indicate the desirability of studying a control patient (Chart 4) to determine whether the results were due to a unique patient situation.

**Control Case.** Patient C. T., a 16 year old white girl convalescing from pneumonia, had been receiving 500,000 units of penicillin per day for 6 days prior to our observations. In order to make the dose response curves obtained from this patient comparable to those obtained from Patient M. C., the same doses of penicillin were used. Injections of 500,000 units of penicillin were given prior to obtaining the curves (Chart 4).

A control curve without caronamide showed the plasma concentration at 15 minutes to be 13.9 units per cc. and at the end of 3 hours 0.87 unit per cc. The following day the patient was given 4 intramuscular injections of penicillin 500,000 units per injection, and 4 oral doses of caronamide, 3 gm. every 3 hours. The plasma concentrations of penicillin were not increased; at 15 minutes there were 10.3 units per cc. and at 3 hours, 0.87 unit per cc. During the definition of this penicillin dose response curve, the caronamide concentrations varied between 17 and 8 mg. per 100 cc. and these concentrations did not inhibit penicillin excretion.

For 5 days this patient received 500,000 units of penicillin per day and 12 gm. of caronamide, then the effect of caronamide was reevaluated. Six injections of penicillin at 3 hourly intervals (500,000 units per injection) and 3 gm. of caronamide were given orally every 3 hours for 6 doses. The enhancing effect upon penicillin plasma concentrations was marked; at 15 minutes the concentration was 29.95 units per cc. and at the end of 3 hours it was still 14.98 units per cc. While these values were obtained the caronamide plasma concentration varied between 45 and 43 mg. per 100 cc. and caronamide obviously inhibited tubular penicillin excretion.

Thus, in the second patient as in the first, there was good correlation between the caronamide plasma concentration and the enhancing effect upon penicillin plasma concentrations.

**Discussion.** Experimental work in animals has shown that caronamide is a pharmacologically active compound<sup>2,8</sup> of relatively low toxicity<sup>5</sup> which is capable of completely suppressing the excretion of penicillin by the renal tubules.<sup>6</sup> In mice<sup>27</sup> it has been shown that the intensity of penicillin therapy can be much increased by the concomitant administration of caronamide and penicillin. This has been particularly well demonstrated by the survival rate of mice infected with Type I pneumococci and typhoid bacilli of the Panama strain. This laboratory background prompted the preliminary clinical investigations with caronamide which have shown that, both in children<sup>14</sup> and

adults<sup>15</sup> that penicillin plasma concentrations can be enhanced from 3 to 7 fold by the oral administration of caronamide. This enhancing effect is noted when penicillin is administered both orally and intramuscularly.

The relative resistance to penicillin of the infecting organism in the case of subacute bacterial endocarditis here described justified the use of the new compound in an effort to enhance penicillin plasma concentrations. There is an increasing awareness that it is almost impossible to maintain a "level" of penicillin in the plasma, but it has been stated that an effort should be made to exceed by 5 times the penicillin concentration which is required *in vitro* to inhibit growth of the infecting organism.<sup>17,19</sup> Treatment of our case in accordance with the above criterion would have required a penicillin plasma concentration of approximately 5 units. To maintain such plasma concentration of penicillin without the aid of some enhancing agent would require enormous quantities of penicillin.

The dose of 4,000,000 units per day was chosen arbitrarily but from the pre-caronamide and the postcaronamide control dose response curves 500,000 units given intramuscularly every 3 hours fell far short of meeting the above requirement. With the aid of caronamide it was possible to elevate the plasma concentration to remarkable heights; 30 to 60 units of penicillin per cc. Such concentrations have seldom been attained with any dose of penicillin alone and to do so in the presence of normal renal function would require at least 10,000,000 units of penicillin or more per day.

Examination of the dose response curves modified by varying caronamide doses shows that the enhancing effect of the same dose of caronamide was not constant. For example, 16 gm. per day showed enhancement of penicillin plasma concentrations on the 15th day (Chart 3) but 9 days later, on the 24th day, no effect was noted. During Course VI when 16 gm. were given (Course III, Chart 4) increased levels were

observed. In the case of Patient C. T. (Chart 4) 12 gm. given in four 3 gm. doses at 3 hourly intervals failed to enhance penicillin concentrations, whereas 18 gm. given in six 3 gm. doses showed marked effect.

The effective dose of caronamide is not uniform in terms of grams per day; enough drug must be given to insure a plasma concentration of caronamide that is adequate to inhibit tubular excretion of penicillin. Although the method used<sup>13</sup> in this investigation to determine caronamide in the plasma is impractical for routine use,\* it has shown a good correlation between caronamide and penicillin plasma concentrations. Both of the patients were regarded as having normal renal function. With plasma concentrations of caronamide less than 10 mg. per 100 cc. Patient M. C. showed no enhancing effect on penicillin levels; similarly, concentrations of less than 20 mg. per 100 cc. in the case of Patient C. T. were ineffective. In both patients concentrations between 30 and 50 mg. per 100 cc. definitely inhibited penicillin excretion. It is suggested that plasma caronamide concentrations between 20 to 30 mg. approximates that required to inhibit excretion of penicillin by normal renal tubules.

Studies already completed indicate that the effective dose of caronamide varies from patient to patient. This is understandable since the pharmacologic action of caronamide is superimposed upon the individual patient's renal function. It is probable that all grades of renal impairment exist in subclinical form and this must be particularly true in the more advanced age groups. It may be anticipated, therefore, that an individual who has some impairment of tubular function will require less caronamide to inhibit completely the capacity of his tubules to excrete penicillin than the patient who has normal tubules. That there is a difference in caronamide requirements for the treatment of individuals of different

ages has already been shown.<sup>23</sup> Further, it has been found that, in children, doses as large as those that have been used in adults, 24 gm. per day, may be necessary to contain the maximal enhancing effect upon penicillin plasma concentration.<sup>14</sup>

The individualization of caronamide dosage is desirable and will be practical when suitable methods for assaying caronamide in the plasma are developed. The method used for the determination of plasma caronamide concentrations in this investigation is impractical for routine use but other methods have already been devised.<sup>11,28</sup> The commonly used PSP test may be a readily available method of determining the effective dose of caronamide. Phenolsulfonphthalein (phenol red) is excreted by the same tubular excretory mechanism by which penicillin, diodrast and para-aminohippuric acid are eliminated, and it has been noted in patients under our care that the excretion of phenolsulfonphthalein is quickly inhibited by adequate dosage of caronamides. It probably can be assumed that, if sufficient caronamide is given to suppress the excretion of this dye, the excretion of penicillin is also being inhibited. Preliminary observations on this point have shown a prompt drop of the normal excretion rate of phenolsulfonphthalein to 25% and 35% under treatment with caronamide and with cessation of caronamide administration, the clearance of phenolsulfonphthalein rapidly returns to normal.

From the available information caronamide appears to have a low order of toxicity. Nausea and vomiting have been noted occasionally when excessively large doses were used, and at least 1 instance of drug fever and diffuse skin rash due to caronamide has been observed.<sup>16</sup> It would be completely unexpected, however, if some toxic manifestations are not observed as use of the compound becomes more widespread.

Heavy caronamide dosage may have produced a transient renal impairment as

\* A 4S hour alkaline dialysate of plasma is analyzed by measuring the ultraviolet absorption at 280 m.u. in the Beckman ultraviolet spectrophotometer. This method is accurate within 10 to 20%.

indicated by cellular elements in the urine, a slight increase in the blood urea nitrogen, and a decrease in urea clearance (Chart 3). These changes occurred during a period of apparent arrest of the subacute bacterial endocarditis and cannot reasonably be attributed to the infection itself. The dental extraction which immediately preceded the onset of the urinary and renal function abnormalities could conceivably have precipitated an acute nephritis, but neither the immediate findings nor the subsequent course support this possibility. It is probable that these manifestations were, indeed, due to caronamide but the rapidity with which the urine cleared and the urea clearance returned to normal indicate the transient character of the renal irritation.

Caronamide is administered in relatively large doses and is excreted in the urine, presumably by glomerular filtration. In order to obviate the likelihood of crystaluria an adequate urinary output (1500 cc.) should be maintained. Caronamide is precipitated in an acid urine (below pH 5.5) and it may be desirable in some instances to alkalinize the urine. The maintenance of an adequate urinary output is probably better protection against renal complications than relying upon the administration of alkalinizing agents.

The rate of disappearance of penicillin from the plasma following an intramuscular dose is, in itself, a good test of renal function which reflects chiefly tubular function. Since 80% of the penicillin in the urine is excreted by the tubules, im-

pairment of the tubules should result in delayed penicillin excretion. The close correspondence between the control curves before and after 2 courses of caronamide therapy extending over 40 days is reasonable evidence that the inhibition of the penicillin excretory mechanism was reversible.

The response of this patient to large doses of penicillin and the concomitant administration of caronamide has been good but no direct claim is made for caronamide in obtaining this result for certainly the doses of penicillin used were far in excess of those which had been tried previously. It may well be that if 4,000,000 units of penicillin alone had been given for 28 days, this patient would have responded similarly. We can say, however, that with caronamide the plasma penicillin concentrations following 1,000,000 and 4,000,000 units per day were increased over those anticipated and obtained with the same doses of penicillin alone.

**Summary and Conclusion.** A patient with subacute bacterial endocarditis due to a strain of *Streptococcus viridans* relatively resistant to penicillin was successfully treated with intramuscular penicillin and oral caronamide.

Even when the dosage employed is measured in millions of units per day, the plasma levels of penicillin can be elevated by the administration of caronamide. The effect of caronamide in the treatment of this patient was equivalent to the injection of additional millions of units of penicillin.

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## CONVULSIVE STATE IN DIABETES

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IN the relatively small but important group of cases of labile diabetes, the frequency of episodes of hypoglycemia and the difficulty of satisfactory control of the glycosuria are well recognized. This group, which is composed almost entirely of younger patients, has always been a severe problem not only to the general practitioner but also to the specialist in diabetes.

The factors that underlie the unpredictability of sudden changes from glycosuria and ketonuria to convulsive states have never been clearly delineated. We have observed 2 patients who tend to shed some light on this situation. Both are young women with "brittle" diabetes, and both had experienced repeated, severe "insulin shocks." One of them died in the hospital; the other is still under observation. The case histories follow:

**Case Reports.** CASE 1. M. B., a white female, was first admitted to The Mount Sinai Hospital in August 1933, at the age of 11, for regulation of her diabetes. The onset of the diabetes had occurred at the age of 6 with polyphagia, polyuria, polydipsia and loss of weight. In the intervening 5 years she had entered other hospitals on 3 occasions because of frequent hypoglycemic episodes, most of which were described as severe. The patient had been raised in a foster home and had never been instructed in the significance of the disease nor in estimating her diet. It was noted that she was not gaining weight and that marked glycosuria was present.

Family history revealed the presence of diabetes in an aunt. Past history was non-contributory; physical examination and laboratory findings other than hyperglycemia and glycosuria were normal. During her

stay in the hospital she was given a diet of carbohydrate (85 gm.), protein (65 gm.), fat (100 gm.), with regular insulin (25-8-25 units) before each of the 3 meals, respectively. Although she was not kept sugar-free on this regimen, and in fact had occasional acetoneuria, she still had occasional severe insulin reactions, one of which was accompanied by a generalized convulsion.

*Second admission:* October 1934. One day after discharge from the hospital she had a severe shock accompanied by convulsions.

*Third admission:* July 1935. She was admitted for tonsillectomy and adenoidectomy because of repeated sore throats. In the interim she had been having occasional insulin reactions. The operation was uncomplicated.

*Fourth admission:* June 1936. This was for a traumatic slipped epiphysis of the lower end of the right radius and a fracture of the right ulnar styloid. Healing was satisfactory.

*Fifth admission:* October 1936. This admission was due to pain in the ear, sore throat and fever. She was disoriented, slightly confused and in obvious diabetic ketosis. The ketosis responded promptly to treatment. Examination revealed a palpable liver edge, normal ocular fundi, and no focal neurologic signs. The patient stated that she had been having frequent, severe nocturnal insulin shocks, as well as occasional dizzy spells. It was now suspected that the picture was complicated by some factor in addition to insulin hypoglycemia. However, in the 2 instances during this admission when she was observed to be unconscious with convulsive movements, she responded to the administration of 50% glucose intravenously. The severity of the diabetes continued to fluctuate; that is, she would pass rapidly from marked glycosuria, even with acetoneuria, to severe hypoglycemic

reaction. When discharged from the hospital she was taking 60 units of protamine zinc insulin daily.

*Sixth admission:* April 1938. The patient was again admitted for frequent nocturnal "shocks," although she was having daily glycosuria. Examination was essentially negative. The blood pressure was 105/75. Laboratory examinations were within normal limits. A roentgenogram of the skull was normal; a roentgenogram of the chest did not show any evidence of increased intracranial pressure and the sella turcica was normal. An electrocardiogram revealed changes in the T waves indicating some involvement of the ventricular musculature.

Further observation in the hospital revealed that there were frequent seizures. Occasionally these were attended by clonic and tonic movements; champing movements of the jaws, rolling of the eyeballs, and biting of the tongue. The attacks were followed by headache. They would cease spontaneously; complete amnesia occurred afterward. The attacks tended to increase in frequency at the onset of menstrual periods. Occasionally the blood sugar was elevated up to 190 mg. per 100 cc. during the episode. A moderate regression was induced by the use of phenobarbital. It was therefore inferred that in addition to hypoglycemic episodes, she was suffering from another factor, probably of the nature of an idiopathic epileptiform state.

*Seventh and final admission:* September 1938. She was admitted in severe ketosis which followed protracted vomiting and neglect in the taking of insulin. She was drowsy, irrational, markedly dehydrated; the blood pressure was down to 76/60. She was treated vigorously and brought out of the ketotic state. She again displayed convulsive manifestations, which most often occurred at night. The blood sugar level varied in different attacks; at times it was normal or elevated, whereas at other times it was low. One nocturnal seizure was actually observed and was described as follows: it was ushered in by an inspiratory crow; the head and eyes deviated to the right, the left arm was extended and the right arm was flexed at the side; there then ensued coarse convulsive tremors of the shoulders and extremities, frothing at the mouth, stertorous respirations and cyanosis; the pupils were dilated and fixed to light; a

Babinski sign was present on the right. Dilantin was started, with no obvious effect.

Several days later, the patient was found dead in bed. Presumably she had died in her sleep, and without any outcry or activity to attract the attention of either the nurses or the patients on the ward. Postmortem blood sugar was 330 mg. per 100 cc., which ruled out hypoglycemia as a cause of death.

*Postmortem Examination.* The body was that of a well-nourished white female, aged 18. There was good panniculus. The heart was normal. The aorta and the larger coronary branches showed scattered, flat, atheromatous plaques with no narrowing of the lumens. The liver weighed 1600 gm., was smooth and showed normal lobular markings. The lungs, gall bladder, adrenal glands, kidneys, uterus and ovaries were grossly normal. The gastro-intestinal tract showed prominence of the lymphoid tissue in the ileum and large intestine. The thymus weighed 35 gm. Microscopically there was congestion of the lungs, liver, spleen and kidneys. The hepatic cells were filled with glycogen. The pancreatic islets appeared normal. There was hyperplasia of the mesenteric nodes. Brain: grossly, the meninges were smooth and shining; the meningeal blood-vessels were moderately engorged. The pituitary was grossly normal. There was prominence of the blood-vessels most marked in the frontal and parietal region, and also present in the pons, but absent in the medulla.

Sections of the frontal lobe, stained with hematoxylin-eosin, disclosed several arachnoid cell clusters in the leptomeninges. The nerve cells of the cortex presented a diversity of degenerative changes. Some were markedly swollen; many, however, were shrunken and contained pyknotic nuclei, while some contained finely granular, deeply staining oval nuclei with an occasional enlarged nucleolus. There were other cells in which it was difficult to distinguish nucleus from cytoplasm. The outline of some cells was irregular and occasionally the cytoplasm was poorly defined. Satellitosis was increased. With Nissl stains, marked central chromatolysis was seen in some areas. The Nissl substance itself was usually finely granular, diffusely scattered through the cytoplasm or concentrated at the periphery at the base of the cell. Some cells stained very faintly. Both cortex and subcortex showed marked

and diffuse gliosis. The blood-vessels were engorged. Similar though less marked changes in the nerve cells were seen in the tegmentum, pons and medulla.

Pathologic diagnosis: degenerative encephalopathy; toxic (?) encephalopathy.

CASE 2. S. K., a white female, was first seen in the Out-Patient Clinic of The Mount Sinai Hospital in 1940, at the age of 13. She was treated for a keloid of the right hand; there were no other complaints or abnormal findings. In May 1943, she was admitted to another hospital in diabetic ketosis which followed 2 weeks of loss of weight, polyuria, polydipsia and pruritus, without preceding incident. She was discharged on a diet of carbohydrate (200 gm.), protein (80 gm.), fat (80 gm.) and 75 units of protamine zinc insulin each morning. Thereafter she attended our clinic. She had repeated insulin reactions and frequent glycosuria. At first her daily requirements for insulin rose to 130 units of protamine zinc insulin, but this was gradually reduced to 70 units. She spent part of the summer of 1943 in a diabetic camp; and here, too, the frequency of insulin shocks was clearly noted.

In February 1944, she was admitted to The Mount Sinai Hospital for diabetic ketosis, and in December 1944 she was admitted for appendectomy. From then until February 1946 she had repeated admissions to several hospitals for either ketosis or shock. Blood pressure, blood cholesterol, blood proteins, chest roentgenograms, neurologic examinations and the eyegrounds were always within normal limits. Occasionally, her urine would show a trace of albumin.

In February 1946, at the age of 19, she was again admitted to this hospital in severe ketosis, following an upper respiratory infection. The ketosis responded well to energetic treatment. However, the diabetes was never too well controlled on a high carbohydrate diet, with the insulin dosage varying from 40 units of protamine zinc insulin to a 2:1 mixture of 60 units of regular insulin and 30 units of protamine zinc insulin. During this hospital stay, she continued to have many attacks of shock which were considered to be related to hypoglycemia. However, many of these were found to occur with a normal or even markedly elevated blood sugar. The seizures were noted to consist of fogging of consciousness, sucking move-

ments of the mouth and tongue, occasionally preceded by a sensation of thirst, and often followed by a variable period of drowsiness. Convulsive movements, tongue-biting, incontinence and frothing at the mouth were constantly absent. There was complete amnesia for these episodes. Neurologic investigation revealed: normal neurologic examination, normal lumbar puncture findings and a normal skull roentgenogram. An electroencephalogram showed alpha waves with frequencies as low as 7 per second, with rare bursts of 3 and 6 per second activity. Hypoglycemic effects on the EEG were ruled out by demonstrating the persistence of these changes even in the presence of marked hyperglycemia.

Dilantin, phenobarbital and tridione were each tried in full therapeutic dosage with no measurable beneficial effect on the frequency or severity of the attacks. She was given a free diet and permitted to have glycosuria, but there was no change in her condition. Because of the fear of possible attacks, she is unable to work. At the present time she is still on a free diet with a mixture of 42 units of regular insulin and 17 units of protamine zinc insulin every morning. The seizures continue at the rate of approximately 1 every 3 days.

An electroencephalogram made in April 1947 again showed alpha waves with frequencies as low as 7.5 per second with rare bursts of 6 per second activity and some single 3 per second waves. Hyperventilation did not increase the amount of slow activity. A record taken 10 minutes after the intravenous injection of 50 cc. of 50% glucose showed the same characteristics.

**Discussion.** It is quite evident that definite abnormalities existed in both cases as demonstrated by the pathologic findings in the one and the electroencephalographic changes in the second. The pathogenesis of these abnormal findings and their relation to the clinical picture is a matter of great importance. Several possibilities are suggested: (1) they are the manifestations of irreversible cerebral changes following repeated insulin hypoglycemia; (2) the changes are independent of the diabetes and are actually an influence in the causation of repeated shocks;



(3) they are evidences of coincidental epilepsies. That repeated hypoglycemic shocks can and do result in irreversible changes in both humans and experimental animals has been amply verified.<sup>1,4,5,6</sup> The actual pathology, while not specific, is sufficiently characteristic to be recognized when the clinical history is known. The changes consist mainly of multiple petechial hemorrhages, proliferation of the glial tissue and widely disseminated injury to the nerve cells. Similar changes are found in cerebral anoxia. Clinically, the relation of hypoglycemia to neurologic symptoms is equally apparent, so much so that it has been aptly likened to an abnormal physiologic decortication. Almost all patients with hypoglycemia have neurologic or psychiatric symptoms of one type or another. Little wonder, then, that permanent changes result, under such conditions, in an organ as sensitive as the brain.

The possibility that the cerebral changes are independent of the diabetes and insulin hypoglycemia, and are important in actually instigating frequent reactions has been suggested by Greenblatt *et al.*<sup>2</sup> These authors recorded abnormal electroencephalograms in 51% of their "problem diabetics" and concluded that the central nervous system plays a leading rôle in the instability. However, they did not rule out the possibility of hypoglycemic changes. Further, such a high incidence of epileptiform tendencies in

diabetics is not borne out by clinical experience or available statistics.<sup>3</sup> Coincidental idiopathic epilepsy must be considered in the differential diagnosis. However, aside from the atypical features of the episodes, the absence of a family history, the lack of response to fairly specific drugs, and the presence of definite pathologic changes in the brain of Case 1 make this highly untenable.

At the present time, we are further investigating the development of the syndrome in our diabetics, as well as the concomitant effect on the personality and associated visceral changes.

The importance of these observations is twofold: (1) The absolute necessity for the avoidance of hypoglycemic episodes is paramount not only for the fright of the immediate episode, but particularly for the prevention of the cumulative irreversible effects of repeated episodes. (2) In the management and treatment of these cases, one must be aware of the possibility of symptoms simulating shock resulting from causes other than hypoglycemia, so that proper treatment may be instituted.

**Summary.** 1. Two cases of labile diabetes associated with non-hypoglycemic reactions are presented.

2. The pathologic and electroencephalographic evidence of cerebral damage were present in these cases.

3. The most tenable assumption is that repeated severe insulin shocks produce irreversible cerebral damage.

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## THE URINARY EXCRETION OF AMINO ACIDS BY A CYSTINURIC SUBJECT\*

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CYSTINURIA is a rare metabolic disease in which cystine stones are deposited in the kidney, cystine crystals may be found in the cornea, conjunctiva, bone marrow and other tissues and as much as 0.5 gm. of cystine<sup>18</sup> may be excreted daily in the urine. Looney *et al.*<sup>16</sup> concluded in 1923 that "The excretion of cystine (*in cystinuria*) is not simply an index of a general disturbance in the metabolism of amino acids but a definite entity confined to cystine," but the observations of several other workers are opposed to this view. Udranszky and Baumann,<sup>19</sup> and other investigators<sup>18</sup> found cadaverine and putrescine in the urine of some cystinuric subjects, while Loewy and Neuberg<sup>15</sup> reported that the excretion of these diamines by cystinuric patients was increased after the ingestion of arginine and lysine. Later workers<sup>4,5,6,11,14</sup> have shown that cystine excretion in cystinuria was increased after the ingestion of methionine, cysteine (but not cystine), glycine, alanine and glutamic acid. It has been reported<sup>2,9,18,20,21</sup> that aspartic acid, leucine and tyrosine were tolerated by cystinuric patients or appeared almost quantitatively in the urine.

Cystine, leucine, tyrosine, lysine and the benzoyl derivative of a substance thought to be derived from tryptophane<sup>1,9,12</sup> have been detected in cystinuric urines, but quantitative data are lacking. For this reason, we determined quantitatively a series of amino acids in the urine of a cystinuric subject with the aid of microbiologic methods.

**Case History.** R. B., a 5 year old white girl, was first admitted at the age of 2 years to the Urological Service of the Hospital of the University of Pennsylvania in 1942. At that time she ran an irregular fever, had pain on urination and voided a cloudy urine. A diagnosis of undulant fever was made. After several months she was discharged. In 1943 she was readmitted to the hospital in coma with abdominal distention and high fever. She recovered from the acute episode, but the pain on urination and the cloudy urine persisted. Roentgen rays taken at this time indicated bilateral urinary calculi. A low fat diet was advised.

The complaints continued and on Aug. 16, 1945, she was readmitted for further study. Her past medical history was non-contributory. She was a full-term baby normally delivered. Her diet was adequate. Development was normal until the stated symp-

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toms began at 20 months. The family history was negative except for 1 aunt with renal disease presumably renal calculi. Physical examination revealed a cooperative pleasant girl who appeared small for her age. Blood pressure was 100/60. Tonsils were atrophied. Remainder of the examination was normal. Laboratory studies were as follows: hemoglobin, 68%; leukocytes, 6500 per c.mm.; urine, acid with 4 to 5 white blood cells per high power field; and urine culture, *Aerobacter aerogenes* and non-hemolytic streptococci. Roentgen ray and intravenous urography confirmed the presence of a right renal calculus and a left ureteral calculus. There was a bilateral hydronephrosis. Cystoscopy under avertin anesthesia revealed a normal bladder cavity. Ureteral catheterization and pyelography confirmed these observations.

A left uretero-lithotomy was performed on Aug. 21, 1945, and the calculus was removed from the dilated ureter. Convalescence was uneventful and a right pyelolithotomy was performed on September 6. The elliptical-shaped calculus from the left ureter measured  $2.4 \times 0.7$  cm. and the roughly triangular calculus from the right kidney pelvis measured  $2 \times 1.9$  cm. The yellow-brown stones had finely granular surfaces and a "maple-sugar" appearance. The calculi were identified as cystine by the Sullivan test. Cystine crystals were found on several occasions. She was discharged on September 23.

She was readmitted on Oct. 22, 1945. The physical examination was unchanged except for well-healed operative wounds. She was placed on a strict diet of 1500 calories daily consisting of proteins (31 to 50 gm.), carbohydrates (119 to 220 gm.), fat (73 to 110 gm.), taken as milk, fruit juices, oatmeal, eggs, graham crackers and butter. Fluids were forced to 2000 cc. daily. On 3 consecutive days 24 hour urine specimens were collected for analysis. She was then placed on methionine, 0.3 gm., 3 times daily for 3 days, in addition to the diet. Urine samples were obtained as before.

Further studies at this time revealed: hemoglobin, 82%; leukocytes, 7200 per c.mm.; urine, acid with many white blood cells per high power field and a trace of albumin, sugar negative; blood urea nitrogen, 10 mg. per 100 ml.; fasting blood sugar, 82 mg. per 100 ml.; carbon dioxide combin-

ing power, 49 volumes per 100 ml.; uric acid, 2.2 mg. per 100 ml.; protein, 6.6 gm. per 100 ml.; chlorides, 106.6 m.eq. per liter; serum calcium, 10.3 mg. per 100 ml.; serum phosphorus, 3.9 mg. per 100 ml.; and alkaline phosphatase, 13.1 Bodansky units. The phenolsulfonphthalein excretion was 62% in 2 hours. Roentgen rays of the long bones showed no evidence of rickets and were considered normal. Intravenous urography demonstrated a residual hydronephrosis with no evidence of calculi.

Upon completion of these studies the child was discharged in good condition. She has remained symptom free and has developed normally.

**PREPARATION OF URINE SAMPLES.** Aliquots of the cystinuric urines were frozen, dried and preserved in this state, the dry material was weighed and dissolved in 0.2 N hydrochloric acid, and the acid solutions were diluted to the original volumes of the aliquots. These solutions and aliquots of the normal urine samples were deproteinized by adjusting the solutions to pH 6.8 and boiling them for 10 minutes. A few drops of acetic acid were added to dissolve phosphates and the mixtures were cooled and filtered. Aliquots taken for amino acid assay were adjusted to pH 6.8 and diluted to the desired volumes. That this treatment was without significant effect on the amino acids in the urines was indicated by assays which gave values for the boiled samples averaging 94 (90 to 100)% of those found for glutamic acid, leucine and valine in the unboiled samples.

Acid hydrolysates of the deproteinized urines were prepared by refluxing 50 ml. aliquots for 6 hours at  $120^{\circ}$  with 6 N hydrochloric acid. The amino acid values were not altered significantly by refluxing the samples for 20 hours under the same conditions. Excess hydrochloric acid was removed by distilling each solution to dryness *in vacuo* at 70 to  $80^{\circ}$ , adding 30 ml. of distilled water to the residual material and redistilling the solution to dryness *in vacuo*. Each residue was dissolved as completely as possible in hot water, the suspension was filtered, the precipitate was washed thoroughly with hot N hydrochloric acid and hot water, and the combined filtrates were diluted to 100 ml. An aliquot of each approximately 0.1 N hydrochloric acid solution was neutralized to pH 6.8, compensated by

the method described previously in this series of papers for the salt estimated to be present in the original urine and that formed by neutralization of the hydrochloric acid, and diluted to the desired volume.

The urine samples, diluted 1:1.5 (see Table 1), were treated with urease to remove urea, a possible interfering substance at this low dilution of urine. The urease was purified essentially by the method of Archibald and Hamilton<sup>3</sup> to remove canavanine and any other free amino acids. A 65 ml. aliquot of urine was adjusted to pH 7, an aliquot of the purified urease solution equivalent to 0.35 gm. of urease was added, and the mixture was incubated at 35 to 50° for 30 minutes. The mixture was boiled immediately for 5 minutes to inactivate the urease and any other enzymes present, 1 drop of

thymolblue indicator. The organisms, the approximate dilutions of the urine samples and the incubation times are given in Table 1.

**EXPERIMENTAL RESULTS.** The daily excretion of 15 amino acids by 7 normal female subjects and by the female cystinuric patient over a period of 5 days is shown in Tables 2 and 3. That these data are of reasonable accuracy is indicated by the mean deviations from the mean of the values at the different levels of samples which averaged 6.4 (3.3 to 10) % for the unhydrolyzed urines and 5 (2.8 to 7.4) % for the hydrolyzed urines. Higher values up to 43% were found for aspartic acid, isoleucine, leucine and threonine in un-

TABLE 1.—ORGANISMS, URINE DILUTIONS AND INCUBATION TIMES EMPLOYED IN AMINO ACID ASSAYS

Amino acid	Urine dilutions		Organism	Incubation time (days)
	Unhydrolyzed	Hydrolyzed		
Arginine	1:2.5	1:5	<i>Lactobacillus casei</i>	3
Aspartic acid	1:2.5	1:20	<i>Leuconostoc mesenteroides</i> P-60	3
Cystine	1:40	1:40	<i>Leuconostoc mesenteroides</i> P-60	5
Glutamic acid	1:2.5	1:40	<i>Lactobacillus arabinosus</i> 17-5	3
Glycine	1:20	1:20	<i>Leuconostoc mesenteroides</i> P-60	3
Histidine	1:40	1:40	<i>Leuconostoc mesenteroides</i> P-60	5
Isoleucine	1:1.5	1:2.5	<i>Lactobacillus arabinosus</i> 17-5	3
Leucine	1:2.5	1:2.5	<i>Lactobacillus arabinosus</i> 17-5	3
Lysine	1:1.5	1:2.5	<i>Leuconostoc mesenteroides</i> P-60	5
Methionine	1:1.5	1:5	<i>Lactobacillus fermenti</i> 36	2
Phenylalanine	1:5	1:5	<i>Leuconostoc mesenteroides</i> P-60	5
Threonine	1:1.5	1:2.5	<i>Lactobacillus fermenti</i> 36	2
Tryptophane	1:20	..	<i>Lactobacillus arabinosus</i> 17-5	3
Tyrosine	1:5	1:5	<i>Lactobacillus casei</i>	3
Valine	1:2.5	1:2.5	<i>Lactobacillus arabinosus</i> 17-5	3

3 N sodium hydroxide was added and the alkaline solution was boiled for 5 minutes to remove ammonia. The hot solution was acidified with acetic acid to dissolve phosphates and to precipitate any proteins present in the urine and the urease. The suspension was cooled and filtered, the precipitate was washed thoroughly with hot water, the filtrate was adjusted to pH 6.8 and the final solution was diluted to 100 ml.

**MICROBIOLOGIC ASSAY PROCEDURE.** The amino acids were determined by the microbiologic procedures and techniques described by Dunn *et al.* in earlier papers of this series except that aspartic acid was determined by the method of Hac and Snell.<sup>10</sup> The final volumes of solutions employed in the assays were 3 ml. per 13 x 100 mm. test tube. Acid production was measured by titration with standard base using bromo-

hydrolyzed urines due primarily to the low concentration of these amino acids.

The possibility that any putrescine (1,4-diaminobutane) and cadaverine (1,5-diaminopentane) present in the cystinuric urine might be measured microbiologically as arginine and lysine, respectively, was investigated. Putrescine was obtained from the Eastman Kodak Company and cadaverine was synthesized as the dihydrochloride from trimethylene bromide by reduction with sodium of the intermediate trimethylene cyanide essentially by the method of Ladenburg.<sup>13</sup> The cadaverine was only about 93% pure since the melting point was 239° to 241° (usual accepted value, 242° to 243°<sup>17</sup>) and the nitrogen content determined by semi-micro Kjeldahl

TABLE 2.—AMINO ACIDS IN NORMAL FEMALE SUBJECTS (MG. PER HOUR)\*

	Subject				Average			
	3		4		5		6	
	Unhyd.	Hyd.	Unhyd.	Hyd.	Unhyd.	Hyd.	Unhyd.	Hyd.
Alanine	10.6	15.5	12.8	22.4	9.9	16.0	14.0	15.5
Aspartic acid	2.0	48.0	5.1	95.0	1.7	100.0	9.2	39.0
Cysteine†	11.6	305.0	106.0	102.0	106.0	660.0	100.0	235.0
Glutamic acid	335.0	121.0	7.9	500.0	6.0	328.0	8.7	602.0
Glycine‡	118.0	11.1	20.0	9.4	81.0	16.4	71.0	63.0
Histidine	3.4	60.0	1.8	43.0	5.8	12.4	4.5	29.7
Isoleucine	10.6	0.0	0.0	89.0	2.7	55.0	11.8	5.5
Leucine	0.7	5.0	2.8	15.0	1.1	10.6	4.8	8.2
Lysine	0.1	20.0	0.9	23.0	1.0	17.2	7.8	20.5
Methionine	8.0	5.0	3.4	29.2	11.0	34.2	5.0	12.8
Phenylalanine	8.1	20.0	27.2	11.0	10.7	21.3	8.3	12.8
Threonine	11.5	12.1	10.6	30.0	13.3	16.7	3.0	2.8
Tyrosine§	3.3	12.1	13.2	25.5	4.0	16.7	3.3	2.8
Valine	603.0	912.0	123.0	508.0	1305.0	1448.0	873.0	1232.0
Total								

\* All of the urines were neutral to litmus except that of Subject 7 which was acid (pH 5.9). The urine of Subject 6 contained a trace of protein; all other urines contained no protein. The urea, methoxides were: (1) 18, 125, 614, 47, 570 and 7.7; (2) 19, 135, 625, 1122 and 9.1; (3) 23, 110, 58, 1270 and 7.8; (4) 33, 120, 63, 1040 and 8.9; (5) 21, 114, 64, 110 and 9.5; hydrolyzed samples minimum since cystine and tyrosine are known to be partially destroyed by treatment with acid in the presence of carbohydrates and other nitrogenous substances.

† Values for hydrolyzed samples minimum since cystine and tyrosine are known to be partially destroyed by treatment with acid in the presence of carbohydrates and other nitrogenous substances.

‡ It is considered of hippuric acid than glycine for *D. metacretoides* P-60 (unpublished data obtained by Ruth Malin in the laboratory of one of us (M. S. D.)).

§ Not determined since tryptophane is destroyed by hydrolysis of the hippuric acid and by the higher activity (per mole) of hippuric acid than glycine for *D. metacretoides* P-60 (unpublished data obtained by Ruth Malin in the laboratory of one of us (M. S. D.)).

TABLE 3.—AMINO ACIDS IN CYSTINURIC FEMALE URINES (MG. PER 24 HOURS)\*

	1072		1073		1074		1075		1076†		Average	
	Unhyd.	Hyd.	Unhyd.	Hyd.	Unhyd.	Hyd.	Unhyd.	Hyd.	Unhyd.	Hyd.	Unhyd.	Hyd.
Alanine	73.0	31.6	112.0	112.0	224.0	265.0	121.0	110.0	130.0	136.0	127.0	137.0
Aspartic acid	1.3	1.3	3.4	32.2	224.0	64.0	1.2	34.0	2.0	27.8	29.0	39.5
Cysteine	123.0	123.0	210.0	125.0	567.0	470.0	2.5	206.0	8.8	149.0	291.0	262.0
Glutamic acid	70.0	70.0	28.8	123.0	369.0	301.0	27.6	92.0	19.3	7.4	10.8	115.0
Glycine	1.2	1.2	164.0	10.3	49.0	55.0	1.3	30.0	1.0	10.7	224.0	160.0
Histidine	78.0	78.0	150.0	18.7	27.1	38.4	238.0	21.1	184.0	16.0	20.4	10.7
Isoleucine	1.5	1.5	22.3	9.4	2.7	30.0	6.2	23.9	11.2	8.2	2.0	16.7
Leucine	1.5	1.5	3.1	12.9	490.0	32.2	10.2	16.2	12.4	16.0	2.9	14.5
Lysine	5.1	5.1	3.0	108.0	25.3	35.8	2.6	23.9	2.1	13.6	7.3	12.5
Methionine	3.1	3.1	164.0	10.3	17.8	30.4	6.7	16.6	5.8	8.9	957.0	1150.0
Phenylalanine	0.9	0.9	3.4	15.3	13.1	25.1	1.0	16.6	1037.0	820.0	1072.0	850.0
Threonine	379.0	379.0	735.0	735.0	1800.0	1800.0	813.0	930.0	1037.0	820.0	1072.0	850.0
Tryptophane	379.0	379.0	735.0	735.0	1800.0	1800.0	813.0	930.0	1037.0	820.0	1072.0	850.0
Tyrosine§	379.0	379.0	735.0	735.0	1800.0	1800.0	813.0	930.0	1037.0	820.0	1072.0	850.0
Valine	379.0	379.0	735.0	735.0	1800.0	1800.0	813.0	930.0	1037.0	820.0	1072.0	850.0
Total												

\* The total ind. volume and grams of total nitrogen, respectively, for the urine samples (numbers given in the parentheses) were: (1072) 550 and 4, (1073) 750 and 8.8, (1074) 805 and 21.8, (1075) 915 and 8.1, and (1076) 175 and 5. The subject ingested 0.3 gm. of dl-methionine 3 times during the day prior to the collection of Sample 1073 and daily on the day of collection.

† Not determined because of insufficient sample.

‡ Not determined since tryptophane is destroyed by treatment with acid in the presence of carbohydrates and other nitrogenous substances.

§ Not determined since tryptophane is destroyed by treatment with acid in the presence of carbohydrates and other nitrogenous substances.

was 14.9% (theory, 16%) for the dihydrochloride. It was found that putrescine did not support the growth of *L. casei* on an arginine-deficient medium and that it did not inhibit the growth of this organism on the same medium supplemented with an adequate amount of arginine. Entirely analogous results were obtained with cadaverine.

**Discussion.** It would appear from the data given in Tables 2 and 3 that arginine, cystine, histidine and phenylalanine in normal female urine and arginine, cystine and lysine in the cystinuric urine were present largely in the unconjugated state since essentially the same values for these amino acids were found before and after hydrolysis of the urines. It may be possible, but is not probable, that conjugated forms of these amino acids with nearly identical activity for the assay microorganisms were present. Since the total amino acids determined after hydrolysis averaged about 45% higher for the normal urines and about 20% higher for the cystinuric urines, it may be concluded that large proportions of amino acids other than those stated existed in conjugated forms. This increase was especially marked in the case of glutamic acid. These observations coincide generally with those reported by Dunn *et al.*<sup>7</sup> for normal male urines.

In our 7 normal subjects the amino acid excretion shows a remarkably uniform pattern, regardless of age differences (age varying from 8 to 33 years).

Marked changes from the normal occurred in our case of cystinuria in the excretion of some amino acids both in absolute and relative amounts. The most significant increases in the unhydrolyzed urines were found for arginine from 16 mg. in normal subjects to 127 mg. in our cystinuric patient, an average for a 24 hour period, and from 1.3 to 14.4% of the total amino acids measured; for cystine from 90 to 290 mg. and from 10.7 to 30.4% respectively; and for lysine from 17 to 230 mg. and 2.4 to 24.2% respectively. In hydrolyzed urines the corresponding

increases were for arginine from 16 to 137 mg. for an average 24 hour period, and from 1.3 to 13.7% of the total amino acids measured; for cystine from 80 to 260 mg. and from 6.4 to 21.7% respectively; and for lysine from 60 to 250 mg. and from 5.2 to 23.7% respectively. The most significant average decreases were for glycine, from 690 to 260 mg. and from 68 to 23% in unhydrolyzed urines; and from 530 to 160 mg. and from 43 to 15% in hydrolyzed urines; for histidine, from 80 to 26 mg. and from 10.8 to 2.9% in unhydrolyzed urines; and from 90 to 38 mg. and from 7.7 to 2.8% in hydrolyzed urines. It is of further interest that the combined excretion of arginine, cystine, glutamic acid, histidine, glycine and lysine averaged about 90 (75.2 to 96.6)% of the 15 amino acids which were determined in all of the normal and cystinuric urines.

The data presented are in accord with the view that in cystinuric patients the metabolism of amino acids may be deranged in several respects and not only with regard to that of cystine. The report by early workers that the diamines, putrescine and cadaverine, which are closely related to arginine and lysine, were excreted in the urine by some cystinuric subjects is in harmony with this conclusion and with our own findings of an increased excretion of arginine and lysine.

In confirmation of previous work,<sup>4,5,6,11,14</sup> ingestion of methionine increased urinary excretion of cystine in our patient.

Recently, Fanconi<sup>8</sup> called attention to the intimate pathogenetic relation of cystinuria to a particular syndrome characterized by stunted growth, rickets, hypophosphatemia, acidosis, glycosuria and high excretion of organic acids, including amino acids. It may be assumed that in cases showing this syndrome the disease develops first as cystinuria, leading to renal injury, followed by other metabolic changes characteristic for impairment of renal function (acidosis, hypophosphatemia, osteodystrophy). In this stage of

the progressive disease, cystine crystals may be found in organs and tissues, and demonstrated *in vivo* by bone marrow biopsy. Fanconi suggests the use of the terms "cystine storage disease," or with reference to the general disturbance of amino acid metabolism—"diabetes acid-aminicus et aminicus." Our patient has not shown the typical Fanconi syndrome, and the pathologic disturbance manifested itself only in the high excretion of cystine and several other amino acids. It is conceivable that the impairment of renal function with consecutive osteodystrophy will develop at a later age.

**Summary.** The daily excretion of 15 amino acids in unhydrolyzed and hydrolyzed normal and cystinuric female urines has been determined by microbiologic methods. Evidence has been presented which indicates that some amino acids are present largely in conjugated and some largely in unconjugated forms. Marked increases from the normal excretion of arginine, cystine and lysine and marked decreases in glycine and histidine occurred in cystinuria. The view of some early workers that there is a general disturbance in the metabolism of the amino acids in cystinuria is supported by the present observations.

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## THE EXAMINATION OF THE HYPERTENSIVE PATIENT

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IN an era of preventive medicine and specific therapy we face a generation of physicians in fervent quest of still another antihypertensive formula, of a bigger and better surgical antihypertensive procedure. It is difficult to find a remedy with which to undo the harm wrought by parental contempt of the laws of heredity. Thus far, essential hypertension remains a familial disease, irrevocably determined by the inheritance of a constitution productive of arterial hypertension, and void of a satisfactory solution.

Meanwhile, the clamor for such a final solution tends to override our sense of diagnostic discrimination in many an instance of hypertension arbitrarily designated as "essential." Occasionally, a patient, for years under supervision because of "essential hypertension," is finally recognized as having another clearly demonstrable disease. It is not known, of course, how many cases wrongly labeled "essential hypertension" never come to a correct diagnosis.

As it is, some physicians subject their hypertensive patients to a wide range of investigation, while many others do not go beyond using the sphygmomanometer. Between these two opposite diagnostic attitudes there is a wide gradation of attempt at differential diagnosis, more or less remote from completeness, depending upon the training, zeal, and inquisitiveness of the given physician.

Under these circumstances, it is deemed purposeful to outline a desirable routine examination of patients who manifest a significant rise of arterial tension. By the same token, it is proposed that the diagnosis of essential hypertension be made dependent upon evidence obtained from such routine examination. Patients not so examined or the cause of whose hypertension is not clearly definable should not

be disposed of by the short-cut diagnosis of "essential hypertension;" they should be regarded as instances of arterial hypertension of unascertained origin.

Last but not least, extensive examination of the new patient afflicted with hypertensive disease serves a much broader purpose than mere etiological classification. It aids in the appraisal of the severity and spread of this disease, reveals its organic distribution and functional pathology, and facilitates prognosis and reasonable treatment.

The following is submitted as a feasible plan of investigation to be followed in cases of arterial hypertension. Several of these headings may offhand seem to be part and parcel of any complete examination. Under all of them, however, special points of pertinent interest are stressed apart from the usual routine which they imply: (1) Family history; (2) individual history; (3) physical examination; (4) urinalysis; (5) blood serology; (6) flat Roentgen ray plate of the chest; (7) electrocardiography; (8) nitroglycerine-test; (9) exercise tolerance test; (10) kidney function test; and (11) urography, and special urological investigation, if indicated by findings obtained from above procedures.

1. FAMILY HISTORY. The family-tree is to be searched for the occurrence of hypertensive disease, vascular accidents, sudden deaths, eclampsia and allied hypertensive manifestations. The body build of the patient should be noted and compared, by careful questioning if necessary, with that of a parent or sibling known to be afflicted with, or to have died of, hypertensive disease. In this connection, the pyknic constitutional type merits particular importance: the short-necked, barrel-chested individual with well arched feet, high horizontal shoulder-girdle, good



muscular endowment, heavy skeletal frame.

The age of deceased parents is significant: patients with moderately severe hypertension may well reach the 6th or even the 7th decade of life; a record of decided longevity in the ancestry practically precludes the existence of grave hypertension of the familial type.

The discovery of one or more cases of congenital heart disease of any type in the family of a hypertensive patient should suggest the possibility of coarctation of the aorta with proximal arterial hypertension.

A dependable history of polycystic kidney in some member of the family prompts the consideration of a similar mechanism being involved in the arterial hypertension of the patient under examination and justifies instituting urographic and other measures for the study of such a diagnostic possibility.

2. **INDIVIDUAL HISTORY.** The past history and symptomatology of the young hypertensive patient need to be scrutinized with a view of possible presence of coarctation of the aorta: one may find parallel manifestations of "cold feet" and headaches in such patients, or the unexpected symptom of intermittent claudication, all explicable on the basis of the underlying anatomical variation of the arterial channels and their respective consequences above and below the coarctation.

Again, in the young hypertensive person, a history of "neuritis" attacks, unexplained cough, and bizarre episodes of abdominal pain, may well suggest a search for the generally elusive entity of periarteritis nodosa.

If the history is one of periodic acute episodes ranging from headaches to collapse, alternating with intervals of freedom from hypertensive complaints, and one is able to elicit also the complaint of unilateral lumbar backache, one should certainly not ignore the possibility of a pheochromocytoma with paroxysmal hypertension. Conversely, however, chronicity alone does not preclude such an

impression. When one suspects the arterial hypertension to be due to such a medullary adrenal neoplasm, it may be helpful to question the patient concerning possible glycosuria in the past on some occasions but not on others: in such patients, simultaneous paroxysms of hypertension and excessive glycogenolytic bouts with glycosuria are likely to have occurred in the past.

The duration of the hypertensive history may be significant. If it coincides with menopause, spontaneous or surgical, and did not precede it by several years, one may suspect the existence of benign menopausal hypertension.

At times, a real and deliberate effort must be made to unearth a psychogenic cause of even very long lasting hypertension. Such an effort at probing the patient's history is especially indicated when the investigator is impressed with the contrast between the long duration and the remarkably benign course of the disorder. Occasionally, such search discloses a death, marital separation, or some other critical event in the patient's past ushering in the onset of complaints.

The importance of such findings in the history is appreciated when "essential" hypertension of seemingly serious severity actually ceases to exist after the provocative background has been eliminated. As an example of this kind the following case is cited.

**Case Reports.** CASE 1. An obese woman 55 years old had a blood pressure up to 225/115, with severe hypertensive complaints of many years duration. She was married to a person not mentally normal, of a family studded with instances of insanity. An insane son born of this union lived at home. He had long been a source of emotional conflict between the patient's maternal attachment, on one hand, and her admission of the urgent need of his confinement at an institution, on the other. Also, her husband was steadily becoming a still further source of perpetual irritation and worry because of growing invalidism demanding constant attention. Significantly, her heart was not enlarged on Roentgen ray examination and

her electrocardiogram was satisfactory. After her husband died and her son finally was placed under institutional care, the patient, now living peacefully with other members of her family, has no hypertensive complaints, and her blood pressure averages 145/95.

One is always impressed with the history of years of anxiety and worry of the small business-man drifting hopelessly between poor credit, not enough stock, too few customers, too much chain-store competition, too many threats of foreclosure. Such an individual's elevated blood pressure, in the absence of definite evidence to the contrary, is not a manifestation of hypertensive disease; rather, it is a neuro-circulatory reflection of his economic maladjustment.

In the history of such instances of "hypertension" one seeks, but does not find, any true episodes of hypertensive disease, such as stenocardia, anginal seizures, or paroxysmal nocturnal dyspnea. Conversely, one distinguishes from such real manifestations of hypertensive heart disease the various neurocirculatory complaints of "inability to breathe," the notorious sighing type of respiration, or the "nocturia" due to nervous insomnia but conspicuous by its absence during a spontaneous or induced restful night. Indeed, such patients often volunteer to supply a history of relative well-being during their hours of work and concentration, while their periods of distress, upon inquiry, may be found to follow excitement and aggravation.

On the opposite side of the ledger, a history of infections, no matter how remote in the patient's past and regardless of their severity, such as sore throat, tonsillitis, or scarlet fever, tentatively suggest the need of ruling out chronic glomerulonephritis with hypertension.

Lead poisoning in the patient's past is significant: it may be the source of hypertension encountered long afterwards, and the kidneys may never have been involved.<sup>2</sup>

Rare instances of "essential" hyper-

tension are known to have been accounted for by head injuries and by cerebral infections which had occurred previously but which have produced neurological changes in the hypothalamus with resulting elevation of the blood pressure.

A history of diabetes mellitus militates against hasty labeling of patient's high blood pressure level as essential hypertension. In the first place, diabetics have a tendency to mild systolic hypertension;<sup>3</sup> in the second place, it is necessary to ascertain the patient's antidiabetic regimen and its efficacy. So many a diabetic person loses his "hypertension" after the diabetes has been brought under satisfactory control, without any other attempt at reducing the arterial tension.

3. **PHYSICAL EXAMINATION.** At the first examination, the finding of an elevated blood pressure should not be accepted with finality, in itself, as a token of hypertensive disease. This is clear in view of the wide range of blood pressure fluctuation under various circumstances and the emotional element often entering into consideration, especially during the first examination by a new physician. One proceeds examining the patient completely and, unable to elicit additional evidence of arterial hypertension, defers a conclusion until it is justified by several readings under basic conditions of physical rest and emotional equanimity.

On each occasion and as a matter of routine, the reflex elevation of the blood pressure following inflation of the cuff should be disregarded. Repeating the procedure slowly a few times, one generally finds the last reading the lowest.

An increased pulse rate detracts from the dependability of the blood pressure reading; it points to a momentary state of excitability with increased systolic arterial tension. This is encountered only too frequently and should not be confused with the picture of hyperthyroidism including tachycardia, systolic hypertension, relatively low diastolic blood pressure, and a wide pulse pressure.

Blood pressure determinations during

the menstrual cycle are often misleading. The same is true for the patient with a distended urinary bladder or one suppressing an urgent need of bowel evacuation. In cases of neurosis with vascular manifestations the blood pressure may be found to be appreciably high because the patient smoked before the examination.

Disparity of the blood pressure readings between the two arms, like the inequality of the radial pulse, should arouse the suspicion of luetic aortic disease or of extensive arteriosclerosis of the aortic arch with involvement of a subclavian artery.

In the young person, the discovery of arterial hypertension in the arms prompts one to examine the arterial circulation of the lower extremities: poorly palpable dorsal arteries of the feet and a blood pressure reading in the popliteal space paradoxically lower than that in the brachial arteries may lead to the diagnosis of coarctation of the aorta. Indeed, the palpability of the posterior tibial and dorsal arteries should be tested routinely in hypertensive patients of any age. In those suspected of having coarctation of the aorta, signs of compensatory collateral circulation should be looked for in the thorax, especially in the subscapular areas.

The physician need not regard this as bending backward to find a case of coarctation of the aorta. It is a fact that such cases are usually discovered accidentally by the roentgenologist, instead of by the clinician.

CASE 2. A white woman, 42 years of age, came to the attention of the writer with the label of "essential" hypertension. She had been subject to episodes of bilateral headache and dizziness for many years. At one time, her 3rd pregnancy had been interrupted "therapeutically" because of hypertension, though 2 previous pregnancies had been entirely uneventful. Several fainting spells had occurred in the past. She complained of irritability, swelling of the ankles on prolonged standing, and increasing dyspnea on mild exertion. Strenuous exertion also caused substernal pain without radiation. During the time since November, 1943, she was examined by many observers.

According to their records, her average blood pressure had been 195/105. Once, an episode of pyelitis prompted one of her examiners to raise the question of anatomical malformation of the urinary tract as a possible explanation of the entire picture, including the hypertension. The impalpability of the dorsal arteries of both feet had been noticed by one of her first attendants. Also, mild exophthalmus remained a constant finding, without any other signs of hyperthyroidism.

During the examination by this writer, the patient complained of choking sensations in recumbent posture, in addition to the symptoms referred to above. On that occasion, her blood pressure ranged from 235 to 240 systolic and from 95 to 105 diastolic. A review of the available clinical data seemed to establish clearly: marked systolic hypertension with but slightly elevated diastolic blood pressure in the absence of aortic insufficiency; uneventful course; appearance of good health despite the long duration of her hypertension; lack of any evidence in support of renal etiology; lack of any other clear-cut etiological data. The label of essential hypertension did not seem to be justified. On the other hand, the choking sensations on lying down, slightly wheezy expiratory breath sounds, the impression of increased dullness beneath the manubrium sterni, and the long known mild exophthalmus, suggested the possibility of a substernal thyroid adenoma. It was for this reason, that a basal metabolic rate determination and a chest Roentgen ray plate were obtained. The metabolic rate was found to be plus 22%, and there was no substernal thyroid lobe visible. However, the Roentgen ray plate showed a considerably widened first portion of the aorta, which may have been the cause of the increased dullness beneath the upper sternum, and very marked erosion of the inferior border of all ribs. Thus, the Roentgen ray findings, not the combined efforts of all clinical attendants, established the diagnosis of coarctation of the aorta.

When the examiner is impressed with considerable obesity in a patient whose blood pressure he found to be abnormally high, he will do well not to diagnose arterial hypertension unless the blood pressure remains high after adequate reduction of the patient's body weight. He

will, however, distinguish that type of hypertension which is associated with obesity of a characteristic distribution, hirsutism, abdominal striae, and, possibly, other manifestations of Cushing's disease.

Precordial auscultation in a patient with high blood pressure often elicits the concomitant accentuation of the second aortic sound. During subsequent examinations, the blood pressure may, of course, vary from time to time. If the unduly loud second aortic sound remains constant, the persistence of this auscultatory observation, regardless of the variation in blood pressure level, connotes hypertensive disease, provided luetic aortitis and thyrotoxicosis have been ruled out.

No hypertensive patient is ever fully examined without visualization of the eye-grounds. Competent ophthalmoscopic examination, because of its diagnostic and prognostic importance, if not possible at the hands of the examining physician, should be requested elsewhere in each instance. In conjunction with other data derived from the study of each case, visualization of the eye-grounds may help in determining not only the extent of hypertensive vascular damage but also the pathogenetic type concerned. For a comprehensive review, the reader is referred to the corresponding chapter of A. Fishberg's "Hypertension and Nephritis."

4. URINALYSIS significantly reveals nothing unusual in uncomplicated essential hypertension. When it discloses albumin in the urine, the possibility of orthostatic albuminuria should be ruled out. For the purpose of microscopic examination, a centrifuged urinary sediment should be obtained. It may provide a clue to the rôle, primary or otherwise, of the kidneys as well as to the extent of the renal disease. One stresses this point in view of the relatively small number of practicing physicians who resort to the use of a centrifuge.

Repeated urinalyses may occasionally produce findings suspicious of pyelonephritis requiring further examination and

urological consultation. Information so obtained may lead to identification and removal of an infected kidney with abolition of the hypertensive mechanism.

5. SYPHILIS, cardiovascular or otherwise, is not known to play a causative rôle in arterial hypertension. Nevertheless, it is wise to institute serological tests in at least a great many cases of hypertension for the following reasons: The constitutional manifestation-time of hereditary hypertensive disease generally coincides with early middle age; so does the occurrence of luetic aortitis. Both produce, at first, the same complaints of stenocardia and mild dyspnea on exertion. In both, there is an accentuated second aortic sound. On the other hand, the height of the blood pressure in early arterial hypertension may not be impressive enough to be of decisive diagnostic aid. Under such circumstances, negative blood tests point to a hypertensive process, while positive results establish the existence of luetic aortitis. Needless to say, however, one occasionally sees both in the same patient.

6. ROENTGEN RAY STUDY OF THE HEART IN HYPERTENSION yields information concerning the size of that organ. In essential hypertension, as in cardiorenal disease due to primary chronic nephritis or nephrosclerosis, the left ventricle is enlarged. However, in primary Bright's disease the heart always increases in size; in essential hypertension, in relatively rare instances, it fails to show any significant change for a period of many years. There has never been any convincing explanation of this phenomenon. In the experience of the writer, this finding of a fairly normal cardiac silhouette in a case of true essential hypertension never justified any prognostic optimism: ultimately, the outlook proved to be commensurate with the sum total of all the other signs and symptoms of the disease. Such a finding does, however, dictate double caution in ascertaining whether or not one is confronted with some benign form of hypertension not productive of cardiac enlargement.

In hypertensive patients a Roentgen

ray plate of the chest is preferable to fluoroscopic examination. It is valuable by comparison with previous as well as with subsequent roentgenograms. Also, one is not likely to visualize fluoroscopically erosions of the ribs in coarctation of the aorta or inconspicuous foci of aortic sclerosis. For forensic purposes, too, the Roentgen ray plate is by far the more eloquent record.

7. AN ELECTROCARDIOGRAM showing a moderate deviation of the electrical axis or mild slurring of the main deflections offers no aid in estimating the heart's share in the consequences of hypertensive disease. A high voltage electrocardiogram alone testifies, at times, to a long-lasting hypertension known to have a mortality<sup>4</sup> of about 40%. Extensive T-wave changes in the 1st and 2nd leads, in the absence of digitalis medication, gross alteration of the QRS complexes with delayed intraventricular conduction, or the electrocardiographic counterpart of *pulsus alternans*, indicate the existence of serious structural lesions and are not a good prognostic omen. Unfortunately, one meets altogether too often with a profuse indulgence in the stereotyped terminology of "myocardial damage" without any real foundation in the tracing; such loose "interpretation" must be discouraged.

Successive electrocardiographic records, like Roentgen ray plates taken at reasonable intervals, may be of considerable value in demonstrating consistently progressive changes of significance. The examiner will do well, therefore, always to compare a tracing taken of a new patient with a previously obtained electrocardiogram, if available.

8. NITROGLYCERINE TEST. The reversibility of high blood pressure is naturally the object of immediate concern to the examiner. One used to hear in the past from some formidable clinicians how fortunate it was for the hypertensive patients that physicians did not have it in their power to lower their blood pressure. Yet, in the natural course of pathological events, such as following a cerebral or a

cardiac vascular accident, one occasionally sees a patient with a lasting spontaneous reduction of the blood pressure not in the least to his harm. Conversely, there is good reason to expect vasospasticity of long duration to bring about in some vital organs a vise-like constriction of the vasa vasorum running along within the arteriolar walls, with impairment of nutrition and necrosis of arteriolar tissue.

For the purpose of testing the fixed or flexible nature of the patient's hypertensive level, the writer has, for several years past, routinely employed nitroglycerine sublingually, from 1/200 to 1/100 grain, depending on the body weight of the patient. No untoward effects have occurred. The method has the advantage of brevity. It obviates the need of resorting to more complicated depressor tests. It offers the same information within a period of about 5 minutes. When the patient is told, in advance, of the ensuing cerebral manifestations of the nitroglycerine effect, he accepts the assurance of their fleeting occurrence with equanimity.

9. EXERCISE TOLERANCE TEST. For the purpose of testing the patient's exercise tolerance, no special devices are needed. With the blood pressure cuff attached to the arm, the patient is observed before and after brusque change from the supine to the sitting position repeated 25 times or less on the examining table. This procedure would seem to be simpler, but no less instructive, than hopping on the floor or negotiating a 3-step footstool.

10. KIDNEY FUNCTION TEST. Ordinarily, it suffices to limit examining renal function to the concentration test and the estimation of the excretion of phenol-sulphonephthalein. Both are easily carried out without the need of referring the patient to any institution or laboratory.

11. UROGRAPHY. In the absence of any instance of hypertensive disease in the family, and without any objective evidence concerning the pathogenesis of the patient's sustained hypertension, extensive urological investigation is mandatory.

Ureteral catheterization should be employed in order to: (1) Secure urine from each side for microscopic and cultural studies; (2) test the secretion of phenol-sulphonephthalein from each kidney; (3) obtain retrograde urograms. Probably, not enough coöperation between the physician in charge and the urologist has been cultivated hitherto for the benefit of obscure cases of arterial hypertension. The urologist's help is not requested often enough.

**Summary.** The finding of high blood pressure in a patient is a challenge to the examining physician. It imposes on him, in each case, the obligation to attempt etiologic study, classification, and overall appraisal of the pathologic process in its entirety.

For this purpose a suitable plan of bedside and laboratory examination is indispensable and should be adopted as a necessary routine. An outline of such examination is here discussed and proposed for consideration.

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# INFARCTION OF AN ENTIRE PULMONARY LOBE WITH SUBSEQUENT ASEPTIC SOFTENING CAUSING STERILE HEMOPNEUMOTHORAX

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It is not generally realized that in rare instances pulmonary infarcts may undergo softening that is aseptic, with subsequent rupture into the pleural cavity, causing sterile pneumothorax. A search of the available literature has revealed only 5 such cases,<sup>1,3,4,6</sup> in only 3 of which the lesion was proven by postmortem examination.<sup>3,4</sup> To this small series we wish to add a sixth case, which shows several unusual features.

The reported cases are listed in Table 1. It will be seen that the proven cases all occurred in patients of about 40 years of age who suffered from heart disease and congestive failure. The source of the embolus was variable, as was the affected pulmonary lobe. The size of both infarct and perforation varied considerably. Perforation occurred in the 2nd or 3rd week following infarction. A positive pressure pneumothorax was the rule, and the character of the pleural fluid varied from serous to frankly sanguinous. In 4 cases,<sup>3,4</sup> including the one here discussed, the patients died shortly after the occurrence of the perforation; in the other 2 cases,<sup>1,6</sup> both of which the etiology of the pneumothorax is open to question, the patients survived—at least until after the pneumothorax had disappeared.

**Report of Case.** A 39 year old colored male (Univ. of Penna. Hospital, No. 146-80, 142), whose family history was not significant, stated that he had been hospitalized at the age of 20 for 6 months for a severe illness, the nature of which is not known. Except for this episode he had enjoyed good health. One year prior to admission, he

was rejected by the Army because of albuminuria. About this time he began to notice weakness, easy fatigability and weight loss. On Oct. 25, 1946, he was suddenly stricken with an attack of dyspnea while climbing a ladder. This forced him to stop work. Abdominal distention developed on November 15, and was accompanied by generalized abdominal pain and constipation. For the first time he noted ankle edema. The next day he was admitted to this hospital.

Physical examination at this time showed evidence of congestive heart failure, with râles in both lungs. There was moderate venous distention, and coarse rhonchi and ankle edema, and the liver extended 3 fingers below the costal margin. The heart was moderately enlarged, and the sounds were weak and muffled. The blood pressure was 114/90 mm. Hg. Respirations were 32 per minute. The pulse was 90, and its quality was poor. The patient was afebrile. There was some abdominal distention.

Laboratory examinations revealed a normal blood count, a negative Wassermann reaction, considerable albumin in the urine and occasional granular casts. Blood urea nitrogen was 16 mg. per 100 cc.; serum bilirubin was 1.6 mg. per 100 cc. The sedimentation rate was 33 mm. per hour, and electrocardiographic studies gave equivocal results.

Röntgen examination of the chest (Fig. 1) showed an enlarged heart with left ventricular preponderance, passive congestion of the lungs, and effusion or thickened pleura on the right side.

The patient was digitalized with improvement of all symptoms, and disappearance of the signs of congestive failure. Examination at this time disclosed an aortic diastolic murmur and a protodiastolic gallop. He seemed in excellent condition, how-

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ever, and was discharged on Dec. 7, 1946, to be followed as an out-patient.

He was seen 1 week later, and seemed to be doing well, but shortly thereafter edema recurred, and he stayed in bed at home. Three weeks before the second admission (about 3 months after leaving the hospital) he developed hemoptysis, followed by pain in the left chest, severe dyspnea, cough and increased weakness. He was readmitted on March 21, 1947. Hemoptysis was considerable, and pulmonary infarction was suspected. The patient was in marked congestive failure, and soon developed jaundice. The Van den Bergh test gave an immediate

gested (Fig. 2). The pressure in the left chest was found to equal 700 mm. of water. On aspiration, 2000 cc. of air and 180 cc. of dark bloody fluid were removed.

The positive pressure pneumothorax was not controlled by repeated aspirations of the left chest or by supportive treatment. The patient died 4 days after admission, about 5 months after the clinical onset of congestive failure.

**Autopsy.** The body was that of a well-developed well-nourished colored male, with a moderate degree of jaundice. Both legs showed pitting edema extending to the groin,

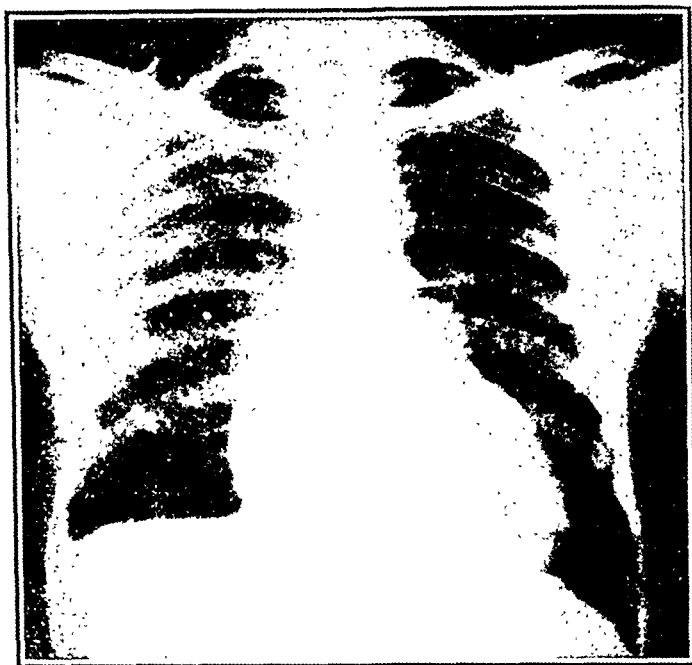


FIG. 1.—Roentgenogram of the chest on first admission. The heart is enlarged and shows left ventricular preponderance. The lungs exhibit slight evidence of congestion and there appears to be thickened pleura or effusion in the right pleural cavity.

direct reaction, and serum bilirubin was found to be 6.8 mg. per 100 cc. The blood urea nitrogen rose progressively to 98 mg. per 100 cc. The right leg was more swollen than the left, but other signs of phlebotrombosis were absent.

Three days after admission, Roentgen examination showed signs of a left pneumothorax with collapse of the left lung, and the presence of fluid at the base. The mediastinum was shifted to the right. Areas of decreased density were seen in the region of the left lower lobe; the lower part of the right lung appeared consolidated and the remainder of the right lung markedly con-

the right leg being considerably more swollen than the left.

The left pleural cavity contained air under tension, and 600 cc. of bloody fluid. The left lung was attached to the apical parietes by a dense fibrous band. The right lung was adherent on all sides by fibrous bands. The layers of the pericardium were thickened and everywhere firmly adherent.

The heart weighed 590 gm. The left ventricle was dilated and hypertrophied, and contained small old adherent mural thrombi. No evidence of myocardial infarction was noted, however. The chordæ tendinæ of the mitral valve were thickened and fused.



The aortic cusps were thickened and calcified and fused, and their free edges were rolled inward. The valves appeared to be both stenotic and insufficient.

The upper lobe of the left lung (Fig. 4)

was almost completely collapsed. There was infarction of the entire left lower lobe caused by a large embolus, broken off thrombus, which completely occluded the principal artery to the lobe. The entire lobe was

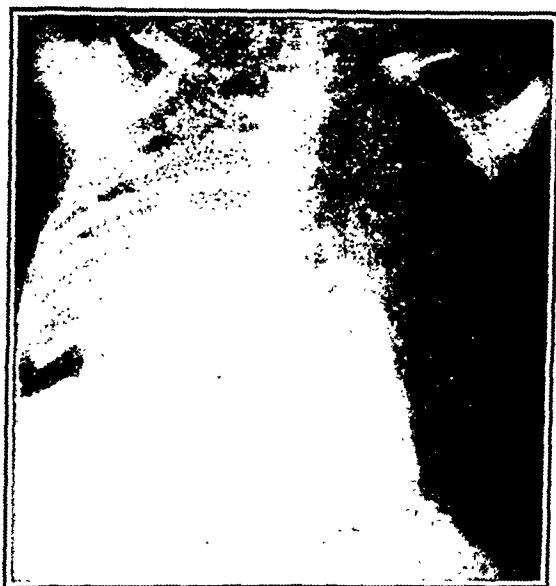


FIG. 2.—Roentgenogram of the chest, shortly before death. There is collapse of the left lung associated with almost complete left pneumothorax. At the base of the left lung are several areas of decreased density. These proved to be due to air in the liquefied portions of the infarcted left lower lobe. There is a collection of pleural fluid on the left. The right lung is markedly congested and there are some areas of consolidation in the lower lung field.



bulky, solid and dark blue-gray on its outer surface. The cut surface was firm and dark red in color. The lower and anterior portion of the lobe was occupied by a large ragged cavity, which communicated with the pleural space by a wide circular opening measuring 6 cm. in diameter. The interior of the cavity was filled with clotted blood and soft debris. Another, smaller cavity, 3 cm. in diameter, was found in the interior of the upper portion of the lobe, the remainder of which had the characteristic appearance of a hemorrhagic infarct.

Microscopic study of the various organs added no information to the gross examination. Of particular interest is the absence of bacteria in the softened areas of the pulmonary infarct, indicating its aseptic character.

**Comment.** A number of unusual features occur in this case, namely the large size of the pulmonary infarct, the aseptic character of the softening, its rupture into the pleural cavity with the causation of



FIG. 4.—Left lung. Note aseptic softening of the infarcted lower lobe. A circular opening on the pleural surface, 6 cm. in diameter, leads into a ragged walled cavity in the left lower lobe, which is completely infarcted. The cavity is filled with debris and clotted blood.

The right lung contained several smaller infarcts in its middle and lower lobes respectively. The other organs showed passive congestion, which was very marked in the kidneys. In the right femoral and iliac veins was a large adherent antemortem thrombus, presumably the site of origin of the emboli.

hemopneumothorax, the jaundice and the high blood urea nitrogen.

It is well known that the size of pulmonary infarcts may vary "from a diameter of about 1 cm. to such a size as to occupy almost the whole of a lobe."<sup>5</sup> In this case the entire left lower lobe was

infarcted owing to occlusion of its main artery.

The ordinary course of events after the occurrence of pulmonary infarction (provided the patient survives a sufficient length of time) is gradual organization of the infarct resulting in a fibrous scar. In very rare instances, however, the necrotic area may undergo aseptic softening with resulting cavitation;<sup>2,7</sup> the present case is an example of this unusual outcome.

in the right base are rather typical of the appearance seen when infarcts occur in a markedly congested lung, as we have observed them in several similar studies by postmortem roentgenograms. The mottled areas of decreased density in the left upper lobe proved to be due to partly aerated lung. The similar but more sharply defined areas seen in the left lower lobe were due to air within the liquefied portion of this infarcted lobe.

TABLE 1.—ANALYSIS OF DATA OF REPORTED CASES

Case	Sex	Age	Underlying condition	Source of embolism	Location of infarct	Size of infarct	Size of perforation	Time of occurrence of perforation	Tension pneumothorax	Pleural fluid
Hayashi <sup>4</sup> No. 7	M	37	Cardiac infarct	Rt. vent.	RLL	Large	Large		Yes	Serofibrin.
Hayashi <sup>4</sup> No. 8	F	40	Nephritis, lft. vent. hyperten., rheum. mitral dis.	Leg	RUL	..	..	..	..	Serofibrin.
Guggenheim <sup>2</sup>	F	37	Coronary dis.	Leg (?)	R	Size of a nut	Size of a lentil	12 days	..	Serous
Daniels <sup>1</sup>	M	20	Typhoid	Leg	L	..*	..	..	Yes	None
Rogers <sup>6</sup>	M	44	Hyperten. ht. dis., card. infarct, apical aneurysm	Rt. vent.	RLL, LLL, RML	Largest, 4 x 4 x 3 cm.	..†	9 days	No	Serous
Rawson and Cocke	M	39	Rheum. aortic dis., femoral phlebotrombosis	Leg	LLL	Entire lobe	6 cm. (diam.)	3 weeks	Yes	Bloody

\* No autopsy.

† Perforation not demonstrated at autopsy.

Jaundice is stated to be an occasional complication of pulmonary infarction, and apparently is a result of hemolysis within the infarct superimposed upon a liver functionally impaired by congestive failure.<sup>2,7</sup> The elevated urea nitrogen noted in this case probably can be explained upon the basis of the release of nitrogenous products from the infarcted area, and the functional impairment of the kidneys owing to chronic passive congestion.

The roentgenological features are of interest. The soft ill-defined character of the shadows cast by the recent infarcts

**Summary.** 1. A case is reported of a 39 year old colored male who developed complete infarction of the lower lobe of the left lung subsequent to long-continued passive congestion. The precipitating cause for the infarction was lodgement of an aseptic thrombus from the right iliac vein. The infarct rapidly underwent aseptic softening with consequent rupture into the pleural sac, leading to hemopneumothorax.

2. The course of events outlined is extremely rare, only 5 previous cases having been found in the world's literature.

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SIGNIFICANCE OF CLINICAL FINDINGS IN CIRRHOSIS OF THE LIVER

A STUDY OF 93 AUTOPSIED CASES

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THIS study is an analysis of cases of fatal Laennec cirrhosis of the liver that came to autopsy at the New York City Hospital in the 26 years from 1920 to 1945, with a comparison of the clinical and pathologic findings in the older and the more recent cases. Among 5916 autopsies reviewed, there were 93 cases in which the death could be directly attributed to cirrhosis. Patients whose hospital stay was less than 24 hours were not included, unless an admission diagnosis of Laennec cirrhosis had been made. The records were divided into 2 groups. Group 1 consisted of 37 cases, dying between 1920 and 1934; Group 2, of 56, between 1935 and 1945.

In both the earlier and the later group, the pathologic anatomic findings were those classically found in cirrhosis, frequently with fatty metamorphosis and superimposed acute hepatic damage. The spleens were enlarged, with increased fibrosis, perisplenitis or chronic congestion. Thrombosis of the portal vein was found in 1 case. Because of the similarity of the lesions in all these patients and adherence to the classical pictures, only the weights of the liver and spleen and the presence of collateral circulation were tabulated. In Group 1, the average weight of the livers was 1324 gm. and the mean weight of the spleens was 332 gm. There was anatomic evidence of collateral circulation in 35%. In Group 2, the livers averaged 1798 gm., the spleens 307 gm. and collateral circulation was found in 66%. These data are tabulated in Table 1.

TABLE 1.—PATHOLOGIC FINDINGS

	Group 1	Group 2
Liver . . . . .	1324 gm.	1798 gm.
Spleen . . . . .	332 gm.	307 gm.
Collateral circulation	35%	66%

*Race, Sex, Age.* As might be expected in a city with a cosmopolitan population, the patients were of various backgrounds and occupations. As far as race is concerned, however, there were 7 Negroes and 86 whites, a ratio of 1:12. This is a smaller percentage than found by Kirschbaum and Shure,<sup>4</sup> who reported a ratio of 1:6. Moon's<sup>6</sup> report to the International Society for Geographic Pathology showed 2 whites to 1 Negro. The average age in the entire series was 54, the average age of both the earlier and the later group falling in the 6th decade. This agrees with the findings of most investigators that cirrhosis is a disease of middle life. Sex differences showed an increasing number of female cirrhotics in the later group. In the entire series, there were 39 females and 54 males. In Group 1, the ratio of males to females was 1.8:1; in Group 2, the ratio dropped to 1.1:1. These data are tabulated in Table 2.

TABLE 2.—ANALYSIS OF RACE, SEX AND AGE

	Race		Sex		Age yrs.
	W	C	M	F	
Group 1 . . . . .	34	3	24	13	53.8
Group 2 . . . . .	52	4	30	26	54.1

*Clinical Data.* Evidence is steadily accumulating that dietary deficiencies are important factors in the etiology of hepatic cirrhosis.<sup>2</sup> In this series, the state of

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nutrition was compared in the 2 groups. It was found that in the earlier studied group, 23 patients (62%) were poorly nourished, whereas 17 (30%) of the second group were in a state of poor nutrition. The use of alcoholic beverages was likewise investigated. Of the total number, 61 were either heavy or moderate drinkers, 8 were teetotalers and the habits of the remaining 24 were unknown.

tite, jaundice and weakness were present more frequently in the second than in the first group. Jaundice was more frequently found by observation, 46% of the early and 64% of the later group.

The most significant finding, however, was the difference in the occurrence of hemorrhage. Whereas only 30% of Group 1 complained of some hemorrhagic phenomenon, 52% in Group 2 had episodes

TABLE 3.—CLINICAL DATA—RANGE OF INCIDENCE IN %

	From history		Physical findings	
	Group 1	Group 2	Group 1	Group 2
Nutrition—Good	..	..	14-38	39-70
Poor	..	..	23-62	17-30
Ascites	22-59	32-57	29-78	42-75
Pain	19-51	26-46		
Dyspnea	13-35	17-30		
Weight loss	11-30	19-34		
Nausea and vomiting	14-30	24-43		
Pedal edema	16-43	19-34	13-35	22-39
Anorexia	11-30	23-41		
Jaundice	10-27	21-38	17-46	36-64
Weakness	11-30	21-38		
Hemorrhage	11-30	29-52	11-30	32-57
Collateral circulation—				
<i>In vivo</i>	..	..	15-41	24-43
At necropsy	..	..	13-35	41-66
Palpable liver	..	..	25-68	42-75
Palpable spleen	..	..	9-24	10-18

Of the other symptoms and objective findings noted in the clinical records, only those which occurred in more than 25% of cases were used for analysis. Except for cough, which was present in 18%, all the other findings were scattered items which could not be compared in the 2 groups. The most frequent complaint and the cause of hospitalization was ascites, presented by 58% of the entire series. Moreover, the incidence was nearly identical in both groups, 59% in Group 1 and 57% in Group 2. On physical examination, ascites was found even more frequently, 78% in the first and 75% in the second group.

The next most common complaint was abdominal pain or distress and was about equally distributed, 51% in Group 1 and 46% in Group 2. Dyspnea, loss of weight, nausea and vomiting occurred less often but in the same relative distribution in both groups. Pedal edema was more frequent in the early group. Loss of appe-

of bleeding. This was further substantiated by the physical findings and at autopsy. Anatomic evidence of collateral circulation was found in 35% of Group 1 and 66% in Group 2.

A palpable liver and spleen were found in about the same proportion in both groups. The clinical data are summarized in Table 3.

*Laboratory Data.* Liver function tests have come into general use only in the last 15 years or so, therefore there are few data in this field in Group 1. The tests to be analyzed in Group 2 are the icterus index, serum cholesterol and cholesterol esters, and the serum albumin and globulin ratio. Of the other tests, there are insufficient numbers to warrant analysis.

The icterus index was determined in 37 cases. In 4 instances, the findings were normal, the highest figure was 200 and the average was 60.

The serum cholesterol and cholesterol esters were determined in 24 cases. The

total cholesterol values were normal (150 to 250 mg. %) in 8 instances, low (below 150 mg. %) in 14, and high (above 250 mg. %) in 2. The cholesterol esters were low (below 60% of the total) in 20 of the 24 cases (83%). Of the 4 cases with normal fractionation 2 had total cholesterol below normal limits, in 1 the total was above normal and in 1 both total and esters were normal. In 23 of the 24 cases, therefore, the cholesterol-ester results were of significance. These data are summarized in Table 4.

TABLE 4.—CHOLESTEROL-CHOLESTEROL ESTER FINDINGS

Esters	Total cholesterol		
	Low	High	Normal
Below 60% . . .	12	1	7
Above 60% . . .	2	1	1

The lowest normal limit for the albumin-globulin ratio regarded as normal in this institution is 1.3:1.6. In this series the test was performed on 21 patients. The average ratio was 1:1.1 and the average total protein 5.12 gm. In 14, the A-G ratio was either less than the lowest limit of normal or the total proteins were under 5.5 gm.

Blood urea nitrogen or non-protein and sugar levels were estimated in most of the entire series. The sugar levels were usually normal. In Group 1, the average urea nitrogen was 24.6 per 100 cc.; in Group 2, the non-protein nitrogen was 35 mg. per 100 cc.

Erythrocyte counts were done in 29 instances. Only 5 were above 4 million. Of the 34 hemoglobin determinations, 26 were below 12 gm. Fifteen of 26 patients had a color index above 1. Only 7 of 30 patients had a white blood count below 10,000.

**Discussion.** The early group, from 1920-1934, represents a more advanced stage of cirrhosis than the later group of 1935-45. The livers were smaller than the normal weight of 1450 to 1750 gm. given by Piersol<sup>7</sup> and the state of nutrition was worse. The reason for this difference in the 2 groups is not apparent.

It is of interest to compare some findings

in the 2 groups. Ascites was the most common presenting symptom in each group, occurred in the same relative proportion and its presence was equally demonstrable by physical examination. Three of every 4 had ascitic fluid when first observed. Lucké<sup>5</sup> also found in a study of early fatal epidemic hepatitis that ascites was a common finding. Ascites, therefore, tends to occur early in the disease and is not, as the older teaching held, a late manifestation.

The mechanism of its production is complex and still a matter of controversy. It is generally said that it is due to a diminution of the colloid osmotic pressure following a change in the plasma proteins, and also to portal hypertension following increasing obstruction to the blood flow through the liver. In the present series, the protein level was determined in 21 ascitic cases. In 14 (67%) the A-G ratio was less than 1.3:1 or the total proteins were less than 5.5 gm. In the same group, 20 of the 21 cases (95%) had either an enlarged spleen or anatomic evidence of collateral circulation. In the entire series, 71 had ascites and 59 of them had splenomegaly. Of the remaining 12 with small spleens, 4 had varices. In other words, 90% of all the ascitic cases from 1920-1945 had evidence of portal hypertension and obstruction to the hepatic circulation. In Lucké's series, ascites often appeared before a drop in the total proteins and the spleens in the ascitic cases were enlarged twice as often as in the non-ascitic. Several workers have also shown that there is no constant relationship between colloidal osmotic pressure and the level of the plasma protein.<sup>1</sup> It is justifiable, therefore, to conclude that portal hypertension has a greater influence in the production of the ascites than does hypoproteinemia.

Jaundice was frequent and sometimes severe. As an early complaint, it was somewhat more common in the second group, but objectively it was very common, was found in almost half of Group 1 and two-thirds of Group 2. The higher

levels were always associated with a greater degree of acute hepatic damage.

The greatly increased incidence of hemorrhage in Group 2 is difficult to explain, but this feature has been noted by other observers.

Of the 3 liver function tests, the most delicate appeared to be the cholesterol-ester fractionation. It was disturbed, with a drop in the ester component, in 96% of the cases. It gave evidence of hepatic damage at an earlier stage than either the albumin-globulin ratio or the icterus index.

**Summary and Conclusions.** 1. Ninety-three autopsied cases of fatal Laennec cirrhosis of the liver are analyzed. They

were divided into 2 groups: one, of 1920-1934, presenting a late stage of cirrhosis, and a second, of 1935-1945, presenting an earlier stage.

2. Ascites was as common in the early as in the late stage of cirrhosis and appears due to obstruction of the hepatic circulation rather than due to hypoproteinemia.

3. In the more recent group presenting excessive stages of cirrhosis, hemorrhage was found much more frequent than in the group representing an older cirrhotic process, for reasons that were not explained.

4. The estimation of the cholesterol fractionation was one of the more delicate tests of hepatic function.

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## INTERFERENCE BETWEEN INACTIVE AND ACTIVE VIRUSES OF INFLUENZA\*

## V. EFFECT OF IRRADIATED VIRUS ON THE HOST CELLS

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IN previous communications from this laboratory<sup>10-14</sup> it has been reported that injection of inactivated influenza virus into the allantoic sac of the chick embryo may prevent the propagation of subsequently injected active virus. Similar observations have been made by others.<sup>25</sup> In these studies the conditions for the optimal production of interfering preparations have been analyzed.<sup>11</sup> Irradiation by ultraviolet light gave more consistent results than heating to 56° C. or formalinization of the virus and the former procedure was therefore adopted for further studies.<sup>12</sup> It was found that the reaction is non-specific in that it occurred between the serologically distinct types of influenza A and B,<sup>13,26</sup> as well as between the influenza viruses and biologically non-related agents such as the viruses of western equine encephalomyelitis,<sup>13</sup> epidemic keratoconjunctivitis<sup>13</sup> and mumps.<sup>15</sup> It was shown by various physical and serologic means<sup>14</sup> that the interfering agent was identical with the inactivated virus particle. In these various studies little or no information has been gathered in regard to the reactions of the host cells. In the present paper some experiments will be related which tend to fill this gap. They were concerned with the localization of the interference reaction, the speed with which the changes are induced and the duration of the altered stage, the effect of irradiated

virus on the development of the host and the adsorption of the inactivated agents on to the host cells.

**Methods and Materials.** The essential techniques employed in the interference experiments have been described in detail in previous papers of this series.<sup>11-14</sup> The technique of the hemagglutination test has been modified during the course of these experiments. In the earlier tests the method of Hirst and Pickels<sup>20</sup> was used; in later experiments the "pattern test" was employed as described previously.<sup>17</sup> For the experiments on the adsorption of hemagglutinin on to the cells of the allantoic sac the technique of Miller and Stanley<sup>24</sup> was adopted.

**EXPERIMENTAL.** *Localization of the Interference Reaction.* It is generally felt that the interference phenomenon is caused by certain changes either on or within the host cells due to direct contact of the cell with the interfering agent. The conditions encountered in the chick embryo permitted a test of this hypothesis and the results reported below serve to substantiate its validity. It was found that injection into the allantoic sac of infected allantoic fluid which had been dialyzed and irradiated by ultraviolet light for 3 minutes produced interference only within this structure, whereas the amniotic cavity remained fully susceptible to infection by active influenza viruses. The reverse experiment, the introduction of irradiated virus into the

\* The work described in this paper was done under a grant from the United States Public Health Service.



amnion with subsequent infection by the amniotic or allantoic routes, gave less clear-cut results. This difference in the results was caused by the fact that injection into the amnion can be made only by passing the needle through the allantoic cavity. This leaves an open communication between the 2 cavities which permits subsequent exchange of either irradiated or active virus. When these effects were minimized by using amounts of the agents close to the minimal effective doses the results become more uniform. A summary of several experiments is presented in Table 1. They show, then, that interference is noted only locally and no generalized protection is obtained by this means.

A simpler, and perhaps more accurate, method was used in later experiments. This involved the use of potent homologous immune serum, against the PR8 strain, for instance, for the interruption of the process of adsorption on to the host cells of the homologous irradiated virus. The state of interference was then measured by the injection of active heterologous virus such as the Lee strain. An experiment of this type is shown in Table 2. As can be seen, 0.2 ml. of anti-PR8 immune rabbit serum injected simultaneously with 0.5 ml. of irradiated PR8 virus prevented interference with the active Lee virus (0.2 ml. of a  $10^{-5}$  dilution) given 2 hours later. Normal serum did

TABLE 1.—THE INTERFERING EFFECT CAUSED BY IRRADIATED INFLUENZA VIRUS—A LOCALIZED ONE ONLY: A SUMMARY OF 3 EXPERIMENTS

1st injection		2nd injection active virus route	Results of hemagglutination test 48 hours after 2nd injection	
Material	Route		Allantoic fluid	Amniotic fluid
None	..	Allantoic Amniotic	Positive Positive*	Negative Positive
Normal allantoic fluid irradiated for 3 minutes	Allantoic	Allantoic Amniotic	Positive Positive*	Negative Positive
	Amniotic	Allantoic Amniotic	Positive Positive*	Sometimes positive† Positive
Infected allantoic fluid irradiated for 3 minutes	Allantoic	Allantoic Amniotic	Negative Negative	Negative Positive
	Amniotic	Allantoic Amniotic	Usually positive‡ Usually negative*‡	Negative Negative

\* Contaminated needle passes through allantoic sac in order to reach amniotic sac; this deposits enough virus to cause infection in practically all allantoic sacs.

† Infection from allantoic sac through hole left by first injection into amniotic sac.

‡ A few negative reactions possibly caused by backflow of irradiated virus from amniotic sac into allantoic cavity.

*The Speed With Which Interference is Induced.* It has been shown previously that interference may be induced rather rapidly in the allantoic sac of the chick embryo.<sup>12</sup> When 12 day old embryos were injected with 1 ml. amounts of irradiated virus while the allantoic sac was flushed with buffered saline solution at a rate of about 15 to 20 ml. per minute for 10 to 20 minutes, the tissue was found to be resistant to subsequent infection with active virus even though the contact of the host cells with the irradiated virus has been very brief.

not affect the interference reaction. When the immune serum was given 1 minute after the irradiated virus the interfering agent was no longer intercepted, so that the subsequently administered active influenza B virus failed to propagate sufficiently to develop measurable quantities of hemagglutinin. In another experiment, the interfering activity was still partially intercepted by serum injected 1 minute after the irradiated virus and only partial interference was obtained. In the same experiment, however, the serum given after 3 minutes failed to prevent interfer-

ence in that experiment. The hemagglutinin titers of 1:64 found by the pattern test in the groups injected with irradiated virus followed by normal serum represented residual, non-adsorbed irradiated virus, since the controls not injected with Lee virus showed the same titers. In addition identification of these hemagglutinins with known immune sera proved them to be of Type A. These residual hemagglutinins were neutralized in the groups of eggs injected with the anti-PR8 immune serum. This serum in itself did not inhibit the growth of the Lee virus, as can be seen in the results obtained in control eggs primarily injected with nor-

was left free in the allantoic fluid of the injected egg. It was conceivable that such amounts of residual, non-adsorbed virus could account for the prolonged protection. Therefore, these experiments were modified as follows: 0.5 ml. of irradiated allantoic fluid (PR8) was injected; after 1 hour, 0.2 ml. of specific immune serum (anti-PR8) was injected to neutralize the unadsorbed particles of virus remaining from the first injection. When eggs thus treated were infected with 0.2 ml. of a  $10^{-5}$  dilution of active heterologous virus (Lee) 2 to 6 days later, it was seen that no measurable concentrations of hemagglutinin were produced

TABLE 2.—SPEED OF PROTECTION BY INTERFERENCE

1st injection, interfering agent	2nd injection		Results of 3rd injection (2 hours after 1st injection)					
	Rabbit serum	Interval between 1st and 2nd injection (min.)	Active Lee virus			Control		
			No. of eggs positive	Hemaggl. titer of pool	Type virus in pool	No. of eggs positive	Hemaggl. titer of pool	Type virus in pool
PR8 allantoic fluid irradiated for 3 minutes	Anti-PR8	0	9/9†	1:1024	B	0/5	<1:2	
		1	0/8	<1:2	..	0/5	<1:2	
		60	0/6	<1:2	..	0/4	<1:2	
	Normal	0	8/9	1:64*	A	4/5	1:64*	A
		1	7/7	1:64	A	4/5	1:64	A
		60	5/6	1:64	A	2/2	1:64	A
Normal allantoic fluid irradiated for 3 minutes	None	..	7/7	1:64	A	4/5	1:64	.. A
	Anti-PR8	60	6/6	1:1024	B	0/4	<1:2	
	Normal	60	6/6	1:2048	B	0/4	<1:2	
	None	..	6/6	1:2048	B	0/5	<1:2	
None	None	..	8/8	1:2048	B			

\* Residual hemagglutinins from first injection.

† 9 out of 9 allantoic fluids positive.

mal allantoic fluid. These data confirm the earlier observations in that they demonstrate that interference is induced rather rapidly, *i. e.*, within 1 minute or less.

*Duration of the State of Interference.* By means of a technique similar to that described in the previous section it could be determined how long the host cells were resistant to infection after contact with irradiated virus. In former experiments,<sup>12</sup> irradiated virus was injected into the allantoic sac of 8 day old embryos and the active test virus was given up to 96 hours after the primary injection. In these experiments not all the irradiated virus was adsorbed by the host cells; some

(Table 3). In other words, the cells of the allantoic sac were resistant to infection for at least 6 days following treatment with the irradiated virus. It was found impossible to test for resistance after longer intervals since the amount and composition of the allantoic fluid changes markedly after the 15th day of total incubation of the chick embryo.

*Effect of the Interfering Virus on the Functions of the Host Cell.* In the course of these experiments 8 day old chick embryos were employed in a number of instances. It was noted in some of these cases that following injection of the more potent irradiated preparations of virus

the embryonic development slowed down. This phenomenon was studied further. A suitable number of 8 day old embryos were candled and the extent of the air sac and of the shadow of the allantoic sac were marked by pencil. After injection of 1 ml. of irradiated virus or normal allantoic fluid, likewise exposed to ultra-violet light, the eggs were returned to the

mental period. On the other hand, those embryos injected with the irradiated virus showed only small increments in shadow and this increase had occurred usually during the first 2 days following the injection. In other experiments, using embryos older than 8 days at the onset, the slight additional growth of allantoic membrane noted in the first 2 days after injection.

TABLE 3.—PERSISTENCE OF RESISTANCE INDUCED BY INTERFERENCE

1st injection, interfering agent	2nd injection		Result of 3rd injection					
	Rabbit serum 1 hour after interfering agent	Interval between 1st and 3rd injection (days)	Active Lee virus			Control		
			No. of eggs positive	Hemaggl. titer of pool	Type virus in pool	No. of eggs positive	Hemaggl. titer of pool	Type virus in pool
PR8 allantoic fluid irradiated for 3 minutes	Anti-PR8	2	0/8†	<1:2	..	0/4	<1:2	
		4	0/7	<1:2	..	0/4	<1:2	
		6	0/10	<1:2	..	0/7	<1:2	
	Normal	2	5/6	1:4*	A	2/6	1:4*	A
Normal allantoic fluid irradiated for 3 minutes	Anti-PR8	2	7/7	1:512	B	0/4	<1:2	
		4	8/8	1:768	B	0/3	<1:2	
		6	9/10	1:384	B	0/4	<1:2	
None	None	2	8/8	1:512	B			
		4	8/8	1:512	B			
		6	10/10	1:384	B			

\* Residual hemagglutinins from 1st injection.

† 0 out of 8 allantoic fluids positive.

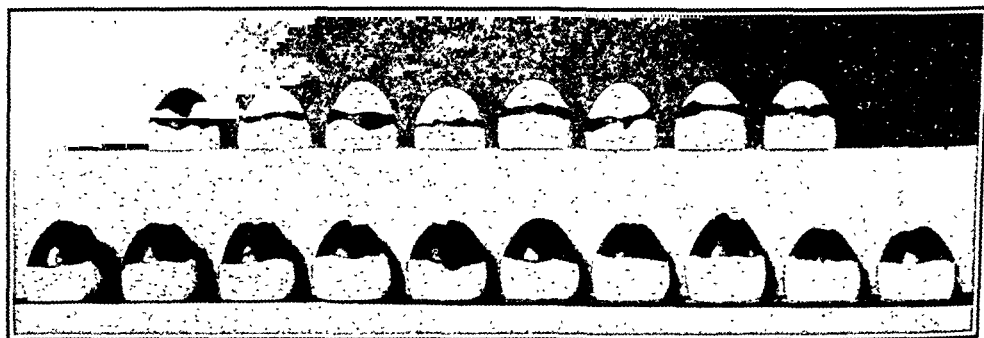


FIG. 1.—Increment in shadow of the allantoic sac in embryos injected with irradiated PR8 virus (upper row) and with irradiated normal allantoic fluid (lower row). The tips are pointing upwards.

incubator and candled daily for 8 days to measure the further development of the allantoic sac. At the end of the experimental period the increase of shadow developed during the 8 days of incubation was blackened and the eggs were photographed as shown in Figure 1. As can be seen the shadow in the eggs injected with normal allantoic fluid almost had reached the tip of the eggs at the end of the experi-

tion of the irradiated virus usually sufficed to bring the shadow of the allantoic sac down to the tip of the egg. In the test shown in Figure 1 only 2 of the embryos in the experimental group had died during the period of the test, none in the group injected with normal fluid. The death rate of the injected embryos in similar experiments was usually of this order. In

no instance have the experiments been carried to hatching time.

Attempts were made to substantiate these observations in this and further experiments by weighing of the wet allantoic sacs of the 2 groups of embryos. However, the figures obtained were found to be not very consistent. They depended on the age of the embryo at the start of the experiment. The results were variable on account of the difficulties encountered in separating the allantoic and amniotic tissues and in removing small traces of allantoic fluid or saline solution used for washing which were caught in pockets

that these sources of error did not affect materially the interpretation of the results, and this technique was adopted, therefore, to obtain some measure of the degree of inhibition of growth. It was found, in addition, that the weight of the chick in the group inoculated with inactivated virus, was reduced as compared with that of the control group inoculated with normal fluid. In eggs of more than 8 days incubation at the time of injection of irradiated virus, the only consistent difference between the 2 groups was in the weight of the embryo. Table 4 summarizes a number of experiments showing

TABLE 4.—EFFECT OF IRRADIATED VIRUS ON EMBRYONIC DEVELOPMENT

Inoculum (irradiated allantoic fluid)		Period of observation Age of embryos (days)	Yield of embryonic materials (average of 8 to 10 eggs per observation)			
Strain of virus	Interference titer*		Allantoic membrane (gm.)	Shell of tip (gm.)	Embryo (gm.)	Allantoic fluid (ml.)
PR8	1:81	8-16	1 3	1.63	11.0	n.t.
normal		8-16	1 44	0 26	15 4	n.t.
PR8	1:81	8-17	1 4	2.1	12.3	n.t.
normal		8-17	1 7	0 27	16.6	n.t.
PR8	1:140	8-16	0.82	1 2	11.3	7.1
normal		8-16	1.84	0.25	15.4	2.75
Lee	n.t.†	8-16	0 66	1.66	6.3	8.0
normal		8-16	2 0	0 45	10.8	2.0
Lee	1:27	8-16	1 7	1 1	9.4	8.2
normal		8-16	1 66	0 7	12 1	4.3
Lee	1:81	8-16	n.t.	1.65	9.3	n.t.
normal		8-16	n.t.	0 62	12.6	n.t.

\* Dilution of irradiated allantoic fluid preventing formation of measurable amounts of hemagglutinins in 50% of the eggs.

† Not tested.

of the membrane. In addition the allantoic sac of the eggs injected with irradiated material sometimes appeared quite edematous. A more consistent measure of the inhibitory effect was obtained when the shell of the tip of the eggs not covered by the shadow of the allantoic sac was weighed, but in that case differences in the thickness of the shell and loss of small fragments of shell during cutting were responsible for some inaccuracies. However, since 8 to 10 eggs were used per group and since the differences encountered in these experiments between the various groups were fairly large it was felt

a marked reduction of embryonic development by the various methods employed. In addition it can be seen that the amount of allantoic fluid remained at a high level in the inhibited eggs whereas the quantities decreased markedly in the controls.

One series of experiments served to establish the fact that only allantoic fluid irradiated for relatively short periods of time gave this inhibition of growth. As seen in Table 5, infected allantoic fluids irradiated for 3 to 5 minutes gave marked inhibition. When exposure for 15 minutes was used inhibition was obtained only occasionally and with longer irradiation

the phenomenon was no longer observed. It is to be noted that these results of inactivation of the growth inhibitor coincide with the inactivation of the interfering property of allantoic fluid. Maximal interference was obtained with fluids irradiated for 1 to 3 minutes, little if any with preparations exposed for 15 minutes and no effect was obtained after an exposure of 60 minutes.<sup>11,16</sup>

ence, on the other hand, could be demonstrated usually when using higher dilutions of irradiated allantoic fluid, *i. e.*, 1:81 or even 1:243. However, the absence of measurable concentrations of hemagglutinins at the end of the experimental period of an interference test does not exclude the propagation of some virus. It indicates merely that the number of susceptible host cells was sufficiently reduced so

TABLE 5.—EFFECT OF PROLONGED IRRADIATION ON GROWTH INHIBITOR  
Yield of embryonic materials  
(average of 8 to 10 eggs per observation)

Inoculum (irradiated allantoic fluid)		Yield of embryonic materials (average of 8 to 10 eggs per observation)			
Strain of virus	Irradiation (min.)	Allantoic membrane (gm.)	Shell of tip (gm.)	Embryo (gm.)	Allantoic fluid (ml.)
PR8	3	0.86	0.90	9.0	7.7
	5	0.70	1.26	7.7	4.5
	15	1.24	0.27	11.9	4.0
	60	1.43	0.30	11.1	5.5
	120	1.20	0.60	12.3	5.8
Control	..	1.65	0.37	11.4	4.5
Lee	5	0.66	1.66	6.3	8.0
	15	1.27	1.05	9.0	3.0
	120	1.78	0.39	11.9	4.1
Control	..	2.0	0.45	10.8	2.0

TABLE 6.—EFFECT OF DILUTION ON GROWTH INHIBITOR

Inoculum (irradiated allantoic fluid)		Yield of embryonic materials (average of 8 to 10 eggs per observation)			
Strain of virus	Dilution	Allantoic membrane (gm.)	Tip of shell (gm.)	Embryo (gm.)	Allantoic fluid (ml.)
PR8	Undil.	0.86	0.90	9.0	7.7
	1:5	0.90	1.43	7.8	5.2
	1:10	1.48	0.96	9.0	7.4
	1:20	1.45	1.16	9.3	7.0
Control	..	1.65	0.37	10.3	4.5
PR8	1:10	1.33	1.43	10.7	5.9
	1:20	..*	0.63	11.7	6.5
	1:30	1.60	0.81	14.1	2.8
	1:40	1.96	0.55	15.3	3.6
	1:80	1.95	0.56	15.1	4.4
Control	..	1.55	0.49	14.8	3.4
Lee	Undil.	0.66	1.66	6.3	8.0
	1:10	1.0	1.13	9.8	6.3
Control	..	2.0	0.45	10.8	2.0

\* Lost by accident.

The inhibitory activity could be noted only with more concentrated preparations of allantoic fluid. As can be seen in Table 6, dilution of the fluid to 1:10 or 1:20, *i. e.*, 0.1 to 0.05 ml. of allantoic fluid, may still produce inhibition of embryonic development. Higher dilutions failed to do so. Some degree of interfer-

ence, on the other hand, could be demonstrated usually when using higher dilutions of irradiated allantoic fluid, *i. e.*, the infectivity titer was less than  $10^{-7}$ .

The fact that not only the allantoic sac but also the chick embryos were retarded in their growth deserved further consideration. This result could have 2 possible

explanations: (a) the decreased growth of the membrane may affect in turn the embryo on account of an insufficient gaseous exchange through the limited expansion of the blood-vessels of the allantoic sac and through the inhibition of other physiologic function of this structure; or (b) the irradiated virus may affect the embryo first and subsequently the development of the allantoic sac. This question was studied in greater detail. First of all, resorption of materials from the allantoic sac appears slow and possibly limited to substances of low molecular weight.<sup>22</sup> As will be shown in the subsequent section of this paper, after an initial loss of hemagglutinin from the inoculum through adsorption on to the host cells the amount of residual virus particles in the allantoic fluid of the injected eggs remains fairly constant, suggesting that no further adsorption or resorption takes place. Another approach to this problem was the determination of membrane and embryo weights at daily intervals following the injection of the irradiated virus. The data obtained suggested that the membrane showed a reduction in growth within 48 hours before significant changes in the rate of the embryonic development were noted. Finally, experiments employing homologous immune chicken serum gave results comparable to those reported in a preceding section of this paper. If the immune serum was given simultaneously with the irradiated virus the inhibitor was neutralized as well as the interfering activity and the development of the embryo was unimpaired. However, when the serum was given 1 to 5 minutes after the irradiated virus so that the antibodies no longer intercepted the interfering activity, the inhibitory effect on the development of the host could likewise no longer be neutralized. Since all free irradiated virus in the allantoic fluid was neutralized by the serum it is strongly indicated that the inhibition of growth is produced by the contact of the irradiated virus particle with the allantoic cells and that the effect

on the embryo is secondary to the inhibition of the growth of the membrane.

The experiments reported in this section show, then, that irradiated virus may exert profound effects on the host cells leading to an impairment of the development of the allantoic sac and in turn of the embryo itself. On prolonged irradiation of the infected allantoic fluids this effect is destroyed, even though the virus particle still may cause hemagglutination and may still be adsorbed on to red cells and on to the cells of the allantoic sac as will be recorded in the next section.

*Adsorption of Virus Hemagglutinin on Host Cells.* It has been shown by Hirst<sup>18</sup> that influenza virus is adsorbed on to red cells and cells of the respiratory tract of the ferret.<sup>19</sup> If the cells support the growth of the virus as in the case of the lung tissue of the living ferret, the virus is not eluted but apparently enters the cells and multiplies. No elution has been noted in chick embryos whose allantoic sac was flushed with saline solution after injection of irradiated allantoic fluid virus,<sup>12</sup> since no hemagglutinin was found in the fluid content of the allantoic sac after an incubation of the eggs for several days. On the other hand, if the host cells do not support the propagation of the virus as in the case of the red cells or the cells of the excised respiratory tract of the ferret, the virus elutes after adsorption.<sup>18,19</sup> The elution of the virus from the red cells is accompanied by changes in the red cells affecting their agglutinability by fresh influenza virus. This has been explained by the loss of "receptor spots" to which the virus attaches itself.<sup>4,18</sup> These receptors are presumably lost or destroyed as a result of the virus action.

Upon injection of known amounts of hemagglutinins into the allantoic sac of 10 to 12 day old chick embryos and collection of the allantoic fluids from the injected eggs as completely as possible after a certain time interval, hemagglutinins were recovered free in the fluid. However, there was always a deficit between the amount injected and the quan-

tity recovered. This missing amount represented, presumably, the amount of hemagglutinin adsorbed on to the cells lining the allantoic sac. The accuracy of the results obtained by this technique depended on 2 factors: the completeness of the collection of the allantoic fluid and the sensitivity of the hemagglutination test. As to the former factor, small quantities of allantoic fluid will be retained in

number of different preparations of infected irradiated allantoic fluid are summarized in Table 7. If the amount of hemagglutinin injected fell below a certain level, the collected fluids were found to give negative results in the hemagglutination tests. In the various experiments conducted with sufficient concentrations of hemagglutinin it was found that the amount adsorbed increased with the quan-

TABLE 7.—ADSORPTION OF HEMAGGLUTININ ON TO THE CELLS OF THE ALLANTOIC SAC

Strain of irradiated virus	Time of harvest (hrs.)	Hemaggl. (units injected)	Hemaggl. (units recovered)	Hemaggl. (units adsorbed)	% adsorbed
PR8	3	512	262	250	49
	6	512	221	291	57
	4	256	86	170	66
	2	256	102	154	60
	2	198	118	80	40
	0 5	192	131	61	32
	2	180	95	85	47
	2	78 5	29	49 5	64
Lee	3	1068	818	250	23
	2	128	13	115	90
	3	128	55	73	57
	2	86	35	51	59
	2	86	38	48	55
	2	38.5	13	25.5	66

TABLE 8.—EFFECT OF CONCENTRATION OF HEMAGGLUTININ ON ADSORPTION ON TO ALLANTOIC SAC

Strain of irradiated virus	Hemaggl. (units injected)	Hemaggl. (units recovered)	Hemaggl. (units adsorbed)	% adsorbed
PR8	180	95	85	47
	90	54	36	40
	45	17	28	62
PR8	192	131	61	32
	96	50	46	48
	48	10	38	79
Lee concentrated 4X	1068	818	250	23
	534	319	215	40
	267	95	172	64
	134	62	72	54
	67	16	51	76

folds of the sac, and care has to be exercised not to break the amnion. The accuracy of the hemagglutination test was somewhat increased in later tests by adoption of the technique of Miller and Stanley<sup>24</sup> who considered differences in titer of about 10% as significant. In spite of these difficulties it is felt that the data to be presented are sufficient to support the points to be made.

The results of tests conducted with a

tity injected. The adsorption amounted to 30 to 90% of the inoculum in these tests. When graded amounts of a given preparation of irradiated virus were injected, it could be shown (Table 8) that an inverse relationship existed between the quantity of hemagglutinin injected and the percentage adsorbed. With the injection of increasingly larger amounts of virus the percentage of hemagglutinins adsorbed decreased. The experiments

have not been carried far enough to reveal definitely whether a saturation point may be reached, *i. e.*, whether the injection of hemagglutinins beyond a certain concentration will not result in further additional adsorption. However, tests suggesting that this may be the case will be briefly discussed at the end of this section.

allantoic fluids of that age altered the hemagglutinating capacity of the agent as well as the pattern formed by the agglutinated cells in the bottom of the test tube. The adsorption of virus on to the cells is independent of the interfering capacity of the virus. Whereas the property of interference is destroyed by irradiation for

TABLE 9.—INFLUENCE OF INCUBATION PERIOD ON ADSORPTION OF HEMAGGLUTININS

Strain of irradiated virus	Hemaggl. (units injected)	Time of harvest	Hemaggl. (units recovered)	Hemaggl. (units adsorbed)	% adsorbed
PR8	96	5 min.	73	23	24
		30 min.	63	33	34
		1 hr.	65	31	32
		2 hr.	61	35	36
		4 hr.	62	34	35
		24 hr.	57	39	41
Lee	86	5 min.	45	41	48
		2 hr.	38	48	56
		6 hr.	31	55	64
		24 hr.	31	55	64

TABLE 10.—EFFECT OF IRRADIATION ON ADSORPTION OF HEMAGGLUTININ

Strain of irradiated virus	Time of irradiation (min.)	Hemaggl. (units injected)	Hemaggl. (units recovered)	Hemaggl. (units adsorbed)	% adsorbed
PR8	0	207	68	139	67
	3	198	118	80	40
	10	184	85	99	54
	30	117	70	47	40
	60	<1			
Lee	3	120	60	60	50
	15	122	70	52	43
	30	132	52	80	61
	45	136	57	79	58
	60	95	16	79	83

The adsorption of hemagglutinin did not increase with time of incubation of the embryos. It did not matter whether the allantoic fluids of the injected embryo were collected 1 hour or 24 hours after injection of the irradiated virus. In each case comparable amounts of hemagglutinin were recovered (Table 9). In other experiments no changes in adsorption were noted up to 72 or 96 hours after injection. However, when the allantoic fluids were collected after 96 hours the results became increasingly more variable on account of the changes occurring in the amount and composition of the allantoic fluids at that stage rendering hemagglutination tests unreliable or impossible. Control tests showed that dilution of virus in normal

15 minutes or longer under the experimental conditions employed the adsorption of the virus on to chicken red cells<sup>16</sup> and on to the cells of the allantoic sac remained unchanged. In other words, as long as hemagglutination remained intact the virus was adsorbed whether it had been irradiated for a few minutes or for 1 hour or longer (Table 10). The question whether adsorption of 1 virus, for instance influenza Type A, prevents adsorption of additional virus of the heterologous Type B has been studied in a few experiments. Ten day old chick embryos were divided into groups of 10 each. The first and second groups received irradiated PR8 virus at time 0. The second was injected again 1 hour later



together with the third group with irradiated Lee virus. The allantoic fluids of all eggs were harvested after further incubation for 1 hour, their volume measured and the content of hemagglutinin determined. The units of hemagglutinins adsorbed in the first group subtracted from the figure found for the second group represents, presumably, the units of hemagglutinin additionally adsorbed and this result should be compared with the result obtained in the third group. The allantoic fluids employed in these experiments showed marked capacities of interference with the propagation of active virus as determined in preliminary experiments. Table 11 shows the results obtained in an experiment of this kind involving 3 different preparations of PR8 virus and 1 of

**Discussion.** The data presented on interference between inactivated influenza and the propagation of the active homologous or heterologous agents in the chick embryo have added to the understanding of the interference phenomenon. The following facts appear to be established: (1) It is the inactivated virus particle which causes interference and not some product resulting from the host-virus interaction. All attempts to separate physically the virus activity from the interfering capacity have failed.<sup>14</sup> However, the interfering property may be based on a different grouping within the virus particle since its resistance to ultraviolet light differs from that of other properties of the virus.<sup>16</sup> (2) Only the host cells directly in contact with the

TABLE 11.—ADSORPTION OF VIRUS BY CELLS PREVIOUSLY EXPOSED TO HEMAGGLUTININS OF THE HETEROLOGOUS TYPE

1st injection (strain)	2nd injection (strain)	Total hemaggl. (units injected)	Hemaggl. (units recovered)	Hemaggl. (units adsorbed)	% adsorbed	Additional hemaggl. (units adsorbed)
PR8 No. 1	..	198	118	80	40	
PR8 No. 1	Lee	198 + 86	151	133	47	53
PR8 No. 2	..	117	70	47	40	
PR8 No. 2	Lee	117 + 86	113	90	44	43
PR8 No. 3	..	184	85	99	54	
PR8 No. 3	Lee	184 + 86	134	136	50	37
	Lee	86	35	51	59	

Lee. As can be seen, the adsorption of the Lee virus was of the same order of magnitude when injected into normal eggs or into eggs previously injected with PR8 virus. These data indicate that additional adsorption can take place on to host cells which had been previously rendered resistant to infection by the primary injection of irradiated virus. In other words, interference does not prevent adsorption. In other experiments when the primary adsorption was more marked, *i. e.*, after the initial injection of larger amounts of hemagglutinin, the evidence for adsorption of the secondarily injected hemagglutinins was negative or doubtful, an observation which suggests that a saturation point may be reached beyond which no further adsorption occurs.

interfering agent are resistant to infection with the active virus, whereas the remainder of the embryonic tissues, if susceptible to infection, remains so. This fact is in agreement with the observations of Kunkel,<sup>21</sup> made in the study of interference in virus infections of plants. (3) Resistance is induced in host cells rather rapidly within a few minutes or even seconds. (4) The host cells treated with irradiated virus remain resistant to infection with active virus for extended periods of time, *i. e.*, for at least 6 days, representing the longest interval which could be studied under the conditions of these experiments. (5) The interfering agent is not without measurable effects on the host cell activities. In the extreme case further growth of the allantoic sac is largely in-

hibited, which, in turn, slows down the embryonic development. (6) Adsorption of active or inactivated virus particles on to the cells of the allantoic sac does not lead in itself to interference, since adsorption is maintained on prolonged irradiation of the virus, whereas the interfering capacity is destroyed after much shorter exposure to ultraviolet light.<sup>16</sup> It is obvious then, that in addition to adsorption, a further step is required to induce interference. Furthermore, after adsorption of irradiated hemagglutinins of 1 type of virus, additional virus particles of the homologous or heterologous type may be adsorbed on to the host tissues, which had been made resistant to infection by the primarily injected agent.

These various observations are in striking agreement with and extend similar data collected by a number of authors in the study of bacterial viruses in their relation to sensitive bacteria. Thus, interference between inactivated and active bacterial viruses has been reported by Luria and Delbrück.<sup>23</sup> The quantitative aspects indicated strongly that the interfering agent was identical with the irradiated virus. Prolonged irradiation by ultraviolet light destroyed the interfering capacity. It was shown that the host cells ceased to multiply upon contact with the irradiated virus.<sup>1,5,23</sup> The inhibition of host cell multiplication occurred within a few seconds after contact of the host cells with the virus.<sup>3</sup> Adsorption of virus on to host cells was not prevented, although they had been rendered resistant to infection by previous contact with homologous or heterologous, active or inactivated virus.<sup>8,23</sup> Finally, Cohen and Anderson<sup>5</sup> found that the oxygen consumption of infected bacteria, or organisms treated with irradiated virus was similar to that of the normal host cells. Preliminary tests conducted by the present authors in collaboration with Dr. Cohen have shown that the oxygen consumption of the chorio-allantoic membrane treated with irradiated influenza virus and showing marked re-

duction in growth was not different from that of normal tissue.

These comparisons show the essential similarity in the activities of 2 widely separated viral agents. Experimentation with the bacterial viruses has the advantage over the influenza host-virus system that one may study the effect of known numbers of virus particles on a known number of bacterial host cells. Thus, it could be demonstrated that 1 single virus particle *per bacterium* altered the host cell in such a way that other virus particles of the homologous or heterologous strain were excluded and further multiplication of the host was prevented.<sup>8,23</sup> It has not been possible as yet to obtain similarly quantitative data in the study of the activity of the influenza viruses in the allantoic sac of the chick embryo. There is no definite proof of the number of virus particles required for the infection of the chick embryo. However, data have been presented that one 50% infectivity dose of a preparation of purified influenza virus corresponded to about 10 virus particles<sup>9</sup> and the chances are that some of these had been inactivated during the process of purification. There is, on the other hand, no information available as yet on the number of susceptible host cells lining the allantoic sac. Further studies will be directed toward solution of this problem.

In the light of these data a number of hypotheses previously suggested by various authors for the explanation of the interference phenomenon can be regarded as invalidated at least for cases where inactivated virus produces rapid changes as recorded in the present paper. Among these one may list: (1) the prevention of spread of the secondarily injected virus by the presence of inflammatory reactions caused by the first; (2) antiviral activity of one virus for another, or the development of antiviral substance in the infected tissues as a result of host virus interaction; (3) the exhaustion by the primarily injected virus of substrates essential for the propagation of the second agent; and (4) a blockade of cell receptors to which the

virus becomes attached prior to entrance into the cells.

There remain 2 hypotheses, both of which can account for some of the observed phenomena. The first assumes the blockade of a "key enzyme" necessary for the propagation both of the virus and the host cell.<sup>8</sup> This hypothesis has been abandoned by one of its authors recently in favor of the second. This hypothesis<sup>7</sup> proposes that changes are produced in the host cell surface by the penetration of 1 virus particle into the interior of the cell which then renders the cell wall impenetrable to other viruses in analogy to the ovum-sperm relationship. However, this comparison certainly is not in agreement with one of the observed facts, the discontinued multiplication of the host. Whereas the hypothesis of the key enzyme can explain interference as well as inhibition of host propagation, the "penetration hypothesis" may account for interference only. It should be emphasized, however, that it has not been definitely proven that inhibition of propagation of the host cell and the interference phenomenon are part of the same mechanism. Although the 2 types of viruses thus far studied in this respect impaired host cell multiplication, other virus infections have resulted in hyperplasia of the host tissues. Whether this stimulation of growth is based on a direct effect of virus or indirectly accomplished by the release of some growth-promoting substance from damaged cells has not been settled as yet. On the other hand, prevention of host cell multiplication by means other than treatment with irradiated virus does not necessarily lead to suppression of virus growth. Spizizen<sup>25</sup> showed that certain glycine compounds

were bacteriostatic but did not prevent virus production, and Anderson<sup>2</sup> showed that bacteria irradiated by ultraviolet light, although no longer multiplying, supported virus propagation. Other substances such as 5 methyl tryptophane prevented both bacterial and viral multiplication which, however, was a reversible reaction in contrast to the true interference phenomenon.<sup>6</sup> It is obvious that these problems require further study.

**Summary.** Further studies are reported on the interference phenomenon observed to occur between influenza viruses inactivated by ultraviolet irradiation and the active agents in the allantoic sac of the chick embryo. They are concerned particularly with the effects of the interfering agent on the host cells.

It has been shown that only cells directly in contact with the irradiated virus become resistant to infection with the active agents. Resistance is induced within less than 1 minute and lasts for at least 6 days. The allantoic sac, in addition, may show impairment of its development, which, in turn affects the growth of the embryo. Host cells rendered resistant by contact with irradiated virus of 1 type may still adsorb additional virus of the homologous or heterologous types. Virus which has lost its interfering capacity by prolonged exposure to ultraviolet light is still adsorbed on to the host cells as long as the hemagglutinating activity remains intact.

These various data are discussed in regard to possible explanations for the interference phenomenon. The striking similarities between the influenza viruses and certain bacterial viruses in their host cell relationships are pointed out.

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## COLD HEMAGGLUTININS IN SICKLE CELL ANEMIA

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SIGNIFICANT titers of cold hemagglutinins were found by Finland *et al.* in 4 cases of acquired hemolytic anemia.<sup>1</sup> Young,<sup>5</sup> in a survey of a large group of individuals for cold hemagglutinins, observed in 3 cases of sickle cell anemia titers of 1:256, 1:4 and 1:4. Wagley<sup>3</sup> has found high titers of cold hemagglutinins in a case of congenital hemolytic icterus and 2 cases of paroxysmal (cold) hemoglobinuria. The purpose of this study is to report the observations on cold hemagglutinins in a large number of cases of sickle cell anemia.

**Materials and Methods.** The method used for titering cold hemagglutinins was that described by Finland *et al.*<sup>1</sup> with variations suggested by Stats and Wassermann.<sup>2</sup> All samples of blood were drawn under sterile conditions at room temperature. Approximately 10 cc. of blood from the patient were placed in a dry, sterile, plugged centrifuge tube and allowed to clot. Several cc. of blood were also placed in a small bottle with 0.5 cc. of an ammonium and potassium oxalate mixture to be used for the determination of the hemoglobin, hematocrit and icterus index. The clotted blood was centrifuged at room temperature and the serum withdrawn by sterile pipette into a sterile, dry tube. Serial dilutions of the serum were made with 0.9% NaCl from 1:10 to 1:2560. Each tube contained 0.5 cc. of the dilution.

Group O cells were washed with 0.9% NaCl 3 times and resuspended in a 0.2% concentration. To each tube containing 0.5 cc. of diluted serum was added 0.5 cc. of the 0.2% erythrocyte suspension. The tubes were shaken thoroughly, packed in

cracked ice and water and stored for 20 to 24 hours in a refrigerator to assure a temperature of circumscribed 4° C. At the end of that time readings were made.

The readings were made against a well-illuminated white background. The tubes were shaken gently 3 to 5 times and read in an arbitrary grade of 4+ to 1+ or negative. A 4+ represented one solid clump of cells remaining after shaking and 1+ the least amount of agglutination grossly detectable to the naked eye. After reading, the tubes were allowed to stand at room temperature for several hours and then re-read. Only tubes in which the agglutination had disappeared were accepted as having been positive. By this technique, agglutination in a titer of 1:40 has been considered significant.

The hemoglobin determinations were made by the Fisher Electrohemometer or the Hellige-Wintrobe method.<sup>4</sup> The hematocrit and icterus index determinations were made by standard techniques.

The amount of sickling was determined in each case by the use of wet preparations. These were made by placing a small drop of freshly drawn venous blood upon a clean, dry slide and covering with a dry cover-slip. The preparation was immediately ringed with petrolatum. The amount of sickling was observed immediately following preparation and at 24 hours by counting the number of sickle cells per 500 red blood cells and expressing the results in percentage.

All patients were questioned as to signs and symptoms of recent upper respiratory infection and the data recorded in Table 1. An attempt was made to correlate cold hemagglutinin titer with the degree of sickling, hemoglobin level, hematocrit, icterus index and severity of disease,† as shown in Table 1.

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† "Severity of disease" is a clinical impression based on the number, frequency and duration of crises, severity of pain and elevation of temperature during the crises, hematologic picture, necessity for transfusion, degree of activity tolerated between crises and presence or absence of leg ulcers.

The control series consisted of 30 colored patients without hemolytic anemia, sickle anemia, or other blood dyscrasias, negative serologic test for syphilis and without a history of recent upper respiratory infection.

prior to and during crisis. No significant change in the titer of cold hemagglutinin (1:320) or other laboratory studies was observed. Another patient (No. 22) was

TABLE 1.—ANALYSIS OF DATA IN 30 CASES OF SICKLE CELL ANEMIA

	Titer						Sickling (%)		Hemoglobin	Hematocrit	Icterus index	Most recent URI before test done	Severity of disease	Most recent crisis before test done
	1:20	1:40	1:80	1:160	1:320	1:640	Immediate	After 24 hrs.						
1	2	1	1	1	1	1	2	55	7.2	22.4	9.0	None	Mod. severe	2 wks.
2	1	1	1	1	1	1	8	55	10.3	32.0	10.0	None	Severe	3 mos.
3	1	1	1	1	1	1	1	30	8.3	25.0	35.0	None	Mod. severe	3 mos.
4	4	3	3	2	1	1	9	95	10.0	20.6	23.0	None	Mod. severe	13 mos.
5	2	1	1	1	1	1	49	95	7.2	29.2	50.0	None	Severe	2 mos.
6	4	4	4	3	1	1	15	85	7.6	30.2	10.0	None	Severe	In crisis
7	1	1	1	1	1	1	52	80	6.2	16.0	20.0	None	Severe	5 mos.
8	1	1	1	1	1	1	32	75	5.8	18.5	35.0	3 wks.	Mild	6 mos.
9	1	1	1	1	1	1	30	70	6.4	19.8	30.0	None	Severe	5 mos.
10	1	1	1	1	1	1	16	70	5.5	23.2	25.0	None	Mild	8 mos.
11	1	1	1	1	1	1	36	75	6.6	22.0	20.0	None	Severe	5½ mos.
12	1	1	1	1	1	1	9	50	9.1	29.0	7.5	None	Mild	None
13	2	1	1	1	1	1	10	55	7.9	27.1	7.5	None	Mild	In crisis
14	1	1	1	1	1	1	0	2	9.1	31.5	7.5	None	Mod. severe	5 mos.
15	..	..	..	..	..	..	25	50	7.0	23.5	18.0	2 wks.	Severe	3½ mos.
16	..	..	..	..	..	..	5	30	10.1	30.0	10.0	1 wk.	No data available	
17	..	..	..	..	..	..	25	100	6.3	21.0	7.5	None	Mod. severe	19 mos.
18	..	..	..	..	..	..	25	90	6.6	23.0	5.0	None	Mod. severe	2 wks.
19	..	..	..	..	..	..	35	100	5.9	20.0	10.0	None	No data available	
20	1	1	1	1	1	1	50	87	6.6	21.0	35.0	None	Mod. severe	4½ mos.
21	4	4	4	2	1	1	25	61	9.1	26.0	20.0	3 wks.	Mod. severe	In crisis
22	4	4	3	1	1	1	2	10	6.3	19.5	15.0	None	Mod. severe	In crisis
23	1	1	1	1	1	1	10	38	5.5	37.0	10.0	None	Mild	In crisis
24	..	..	..	..	..	..	74	81	7.2	25.2	10.0	None	Severe	7 mos.
25	..	..	..	..	..	..	2	14	6.7	22.4	20.0	2 wks.	Mild	None
26	2	1	1	1	1	1	1	5	11.0	36.0	25.0	None	Mild	None
27	4	2	1	1	1	1	9	59	9.7	28.2	10.0	None	Mild	18 mos.
28	3	1	1	1	1	1	41	77	9.5	32.0	25.0	None	Mild	None
29	..	..	..	..	..	..	14	78	8.4	26.0	25.0	None	Mod. severe	In crisis
30	..	..	..	..	..	..	8	24	11.7	34.0	7.5	None	No data available	

**Results.** Table 1 shows the distribution of titers for cold hemagglutinins in 30 cases of sickle cell anemia. Eighteen cases (60%) showed a titer of 1:40 or over; 11 cases (36%) had a titer of 1:80 or higher; 4 cases (13%) had a titer of 1:160; 4 cases (13%) had a titer of 1:320; 1 case had a titer of 1:640. No correlation could be made with the degree of sickling, hemoglobin, hematocrit or icterus index. In 21 cases, the date of the last crisis could be precisely determined by hospital records. In these cases no correlation could be established between the recency or severity of the attacks and the titer of the cold hemagglutinin.

Three control cases (10%) showed a titer of cold hemagglutinin of 1:40, but none showed a titer of 1:80.

In the course of these experiments, 1 patient (No. 6) was observed 2 weeks

observed 10 months prior to crisis, at which time she showed a maximum titer of cold hemagglutinin of 1:40. During crisis a maximum titer of 1:640 was reached. There was no striking change in other laboratory findings. A third patient (No. 23) was observed to have no titer of cold hemagglutinin 2 weeks prior to crisis. During crisis a maximum titer of 1:40 was demonstrated.

**Conclusion.** The cold agglutinins in a series of 30 cases of sickle cell anemia were determined. Of these cases, 60% showed a titer of 1:40 or over; 36% had a titer of 1:80 or over. A significant titer could not be correlated with degree of sickling, hemoglobin level, hematocrit, icterus index, the severity of the disease or consistently with the elapse of time since the last crisis.

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## PROPYLTHIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM

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THE use of propylthiouracil over a 14-month period from December, 1945, to March, 1947, has convinced us that it is decidedly superior to thiouracil in the treatment of hyperthyroidism. In our opinion propylthiouracil appears to be as effective as thiouracil in about half the dose and is much less toxic in its side effects. These findings are in agreement with those of previous reports.<sup>1,2,3,5</sup>

The present paper presents a brief summary of the therapeutic properties of thiouracil and discusses some of our experiences in treating 218 cases of hyperthyroidism with propylthiouracil. It deals briefly with a few of the aspects of the problem, including its safety, effectiveness, and required dosage, and contains a note regarding the concurrent use of small doses of iodine. The final place attained by any medical or surgical means for the clinical management of hyperthyroidism depends on at least one other important factor, namely its ability to produce a lasting remission or permanent cure. Insufficient time has elapsed in the use of propylthiouracil to make any sound statements on this phase of the problem. Time may reveal, however, that this point is not very important, provided the drug proves to be safe to use for long-continued periods.

**THIOURACIL.** Thiouracil was used earlier and has been used much more widely than propylthiouracil. Before thiouracil was placed on the market it had been used in the treatment of more than 5000 patients and had been abundantly proved to be an effective means of controlling any type of hyperthyroidism with

the possible exception of thyroid crisis, in which its action was too slow. Hyperthyroidism of acromegaly may also prove to be an exception.

The rate of response to thiouracil is not easily predicted. A fall in basal metabolic rate of 1% per day is seldom exceeded, while at the opposite extreme some patients fail to show any response of consequence for four or five months but later are well controlled. In general, hyperthyroidism associated with the small diffuse goiter responds quickest and that associated with the large nodular goiter slowest. The prolonged use of large doses of iodine preceding thiouracil therapy is a barrier to prompt response.

The main disadvantage of thiouracil is that toxic effects such as fever, rash, or nausea occur in 10 to 15% of the patients. Much more serious is the agranulocytosis which has been seen in 2 to 3%; death from this occurs in 0.5 to 1%. In addition, a striking enlargement of the thyroid has occurred in some patients. These effects have prevented the use of the drug in many instances. Though its effectiveness is high, the mortality rate from propylthiouracil is comparable to that of thyroidectomy in the hands of the most skillful surgeons. Thiobarbital, which is much more potent in its antithyroid action, has similar toxic effects.

The rate of permanent remission of hyperthyroidism with thiouracil therapy has not been determined. One of the best estimates is that of Williams,<sup>6</sup> who reported a remission rate of 50% in 100 cases. It is possible that the general tendency toward early withdrawal of the

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drug because of the risk of toxic effects may have reduced the number of permanent recurrences.

*Present Usefulness of Thiouracil.* One of the chief advantages of this therapy is the production of complete control of hyperthyroidism and the fact that almost all patients are able to follow their usual occupations. The complications of hyperthyroidism are controlled as well by thiouracil as by thyroidectomy.

Since thiouracil is no safer than surgery in uncomplicated moderate hyperthyroidism, and since it has not been proved to cause remissions as often as thyroidectomy, its greatest benefit is the reduction of surgical risk in selected patients. If used in severely toxic patients, those with cardiac failure, those who are weak from long-standing disease, or in those of advanced age, many will become good surgical risks. In those who remain bad risks continued therapy may be warranted. By limiting the use of thiouracil in this way the mortality of thyroid surgery has been reduced almost to the vanishing point, but the mortality rate of the drug itself remains unchanged.

*PROPYLTHIOURACIL.* It was evident from experience with thiouracil that a safer drug was needed, and 6-n-propylthiouracil appears to have supplied this need.

Astwood,<sup>1</sup> in the first 100 cases reported, found 4 instances of transient pruritus, 2 of transient headache, and 1 of transient arthralgia. One of his patients died during therapy apparently from progressive hepatic failure due to extensive cirrhosis.

Among our 218 patients, manifestations which we attributed to the toxicity or sensitivity to propylthiouracil were seen in 7 patients. Three had mild reactions: nausea, arthralgia, arthralgia and numbness. The drug was continued in all 3 of these patients. The first patient was nauseated while taking 300 mg. a day, but could take 200 mg. without discomfort. In the patients who complained of arthralgia or numbness of the forearms

and hands, the symptoms disappeared while the drug was continued. No hypothyroidism or any evidence of organic nervous disease could be demonstrated in them. Propylthiouracil was discontinued in 4 patients. One patient developed a severe dermatitis simulating the exfoliative type while taking 50 to 150 mg. a day after 34 weeks of treatment. Skin testing or further trial of the medicine has been delayed in this case because of the severity of the dermatitis. The second patient complained of numbness of the extremities. This probably was a toxic effect, since no other cause was found to explain it. One showed a fall in the granulocyte count to as low as 25% on repeated trials of 75 to 150 mg. per day, so the drug was finally discontinued after 22 weeks of treatment. This case has been reported.<sup>2</sup> In one patient the drug was discontinued because of urticaria, and thyroidectomy was performed. One patient died at his home while taking the drug. He was 65 years old, had a nodular goiter and poor cardiovascular status. One day, without having complained more than usual, he vomited, became extremely weak, and died within a day. He had no fever. Blood counts were not made. Unfortunately, news of his death did not reach us at once. In spite of contact made with his relatives and the physician called in, no further information could be obtained, and the cause of his death was never ascertained. The meager information we received did not appear to point toward a toxic reaction, but such a possibility cannot be entirely excluded.

The final appraisal of the side effects of propylthiouracil, based on 218 separate clinical trials covering an average of 8 months per patient and using doses from 50 to 500 mg. a day, confirms to us the fact that it is a relatively non-toxic drug. To date the maximum doses used have caused no more toxic effects than have followed the small doses. There were no fatalities, 3 minor reactions which did not interrupt treatment, and 4 reactions which necessitated stopping the drug. Agranulo-

cytosis did not occur. Consequently, we have discontinued the routine practice of taking weekly white blood counts. In prescribing the drug the possibility of a toxic effect is explained to the patient, and it is suggested that a white blood count be made if a sore throat or unexplained fever occurs.

*Effectiveness and Required Dose.* The speed of response is an important consideration. The continuance of hyperthyroidism in a patient with complicating heart disease, diabetes, or tuberculosis may lead to an irreversible downhill course. Even without concurrent disease it is highly desirable to lower the basal metabolic rate as quickly as possible. At best the treatment covers several months, and the patient may be discouraged and lose contact with his physician if the results are too gradual. For this reason, the smaller initial doses of 150 mg. per day, as recommended in earlier publications,<sup>2</sup> have been replaced by doses of 300 mg. or more per day in moderately severe and in severe hyperthyroidism. Somewhat smaller doses may be sufficient for maintenance, but even this must be taken as a guarded conclusion.

All of our patients have remained ambulatory and have been treated as office patients except those who were seriously debilitated by complications such as cardiac decompensations of severe degree. Almost all others continued to work or to carry on their usual activities. The basal metabolic rate was determined at intervals of 4 weeks. A few patients received iodine in doses of 10 to 30 mg. per day in addition to propylthiouracil for comparative purposes. When the metabolic requirements were high and there was a tendency to weight loss, diets supplying as much as 4000 calories per day were prescribed and vitamin B complex was given to a few. Sedatives, such as phenobarbital, were used on doses of  $\frac{1}{2}$  gr. 3 times a day in many. Otherwise no other medication was given except that which was necessary to treat a complicating disease.

Eighty-seven patients who had responded with complete control of their symptoms and basal metabolic rates were used to compare the speed of effect of the drug at different dosage levels. The remainder were eliminated from this part of the study for various reasons. Some had been treated for too short a time; in some propylthiouracil was used to maintain a remission which had been effected by thiouracil, iodine, or x-ray; a small group failed to take the drug as prescribed, and finally in some the basal metabolic rate did not show an adequate response due to complicating factors such as asthma or poorly compensated cardiovascular disease and thus was not an accurate indication, despite control of the hyperthyroidism.

Of the 87 patients 51 had diffuse goiter, 22 had nodular goiter, and 14 had recurrent or residual hyperthyroidism following previous operation. The usual sex incidence was present. The original basal metabolic rate ranged from +19 to +79%. Complicating disease included rheumatic and arteriosclerotic heart disease, syphilis, diabetes, and pernicious anemia.

The dose of propylthiouracil varied from 50 to 400 mg. a day. Early in the study, doses of 75 or 100 mg. per day were common, but as our experience increased we gradually raised the dose to the higher levels in order to obtain a more rapid response. To study the comparative effectiveness of various doses, these cases have been arbitrarily divided into two groups: (1) those receiving less than 150 mg. per day and (2) those receiving 150 mg. or more per day.

In the 48 patients with diffuse goiter receiving 150 mg. or more a day, there was an average fall of basal metabolic rate of 2.91 % per week, while in 3 patients with diffuse goiters receiving less than 150 mg. a day the fall was 2.64 % per week. The most rapid response was seen in a patient having recurrent hyperthyroidism with a basal metabolic rate of +60% which fell to -11% in six weeks, an average of 11.8% per week. The dose was 200 mg. per day.

In the 15 patients with nodular goiters on the higher dose, the fall was 2.49% per week as compared with a fall of 1.74% per week in 7 patients on the smaller dose. In recurrent or residual hyperthyroidism the fall was 2.96% per week in 8 instances while it was only 1.18% per week in 6 patients receiving less than 150 mg. per day.

in continuing it. The basal metabolic rate in many instances drops rapidly down to +20 or +15% and slowly from that level to zero. Often, to be sure, a good response will be made on 150 mg. until the basal metabolic rate reaches +15%, and then more than 200 mg. per day is necessary to relieve the remaining signs of hyperthyroidism. In a few patients the

TABLE 1.—RESULTS OF DIFFERENT DOSAGES OF PROPYLTHIOURACIL

	Group 1. (Less than 150 mg. per day) 16 patients	Group 2. (150 mg. or more per day) 71 patients
Average fall in B.M.R. per week . . . . .	1.73%	2.82%
Average original B.M.R. . . . .	23.5%	+38%
Average duration of treatment before B.M.R. returned to normal . . . . .	13.6 weeks	13.6 weeks

Our data were analyzed with respect to effective dose range in another way. For this purpose an effective dose was defined as one which produced a progressive fall in basal metabolic rate of 2% or more per week to within normal range. An effective dose might take more than 3 months at this rate to produce a fall in the basal metabolic rate to within normal range, depending upon the height of the metabolic rate at the beginning of the test. If 3 months passed, however, and a rate of fall of basal metabolic rate less than 2% per week still persisted the dose employed was called ineffective. A single patient might fail to respond adequately to 150 mg. or even 200 mg. per day and yet respond well to 300 mg. or more. Thus more than one test might be made on 1 patient. In the following figures 158 such tests are represented. The results are summarized in the following table.

TABLE 2.—ESTIMATED EFFECTIVENESS OF DIFFERENT DOSAGES OF PROPYLTHIOURACIL

Daily dose	Total No. of tests	Effective	Per cent effective
150 mg. and less . . .	50	29	58.0
200 mg. and less . . .	111	97	87.4
300 mg. and less . . .	158	152	96.3

Thus a dose of 300 mg. per day is seen to be ineffective, if defined in these terms, in only 3.7% of these patients. In them, doses higher than 300 mg. per day were required. We have seen little disadvantage in using 300 mg. as the initial dose or

dose had to be raised even to 400 mg. or more to obtain a normal metabolic rate. Four hundred milligrams or more per day have been used at some time during the treatment of 25 patients.

Frank myxedema occurred twice, and definite symptoms of hypothyroidism appeared in 5 other patients. Desiccated thyroid was given to control this complication, and the propylthiouracil was continued. We wished to maintain the depressive effect on the goiter in the hope of increasing the chance of securing a permanent remission. Only 2 patients showed significant enlargement of the thyroid. One of these was a young woman who was pregnant, the other a boy 17 years of age. We have not been impressed by the presence of a lethargy or drowsiness which might be regarded as an effect of the drug apart from the hyperthyroidism.

We interpret these data to mean that 300 mg. per day of propylthiouracil is near the ideal dose to be used in active treatment of hyperthyroidism. Although some patients respond to smaller doses, a dose of 300 mg. or more a day has been necessary in 34% of the total number of patients in order to lower the basal metabolic rate to normal range. If toxic results on doses of 300 mg. or more per day are shown to be more frequent in further studies, the routine use of this initial dose will be modified. If such circumstances arise,

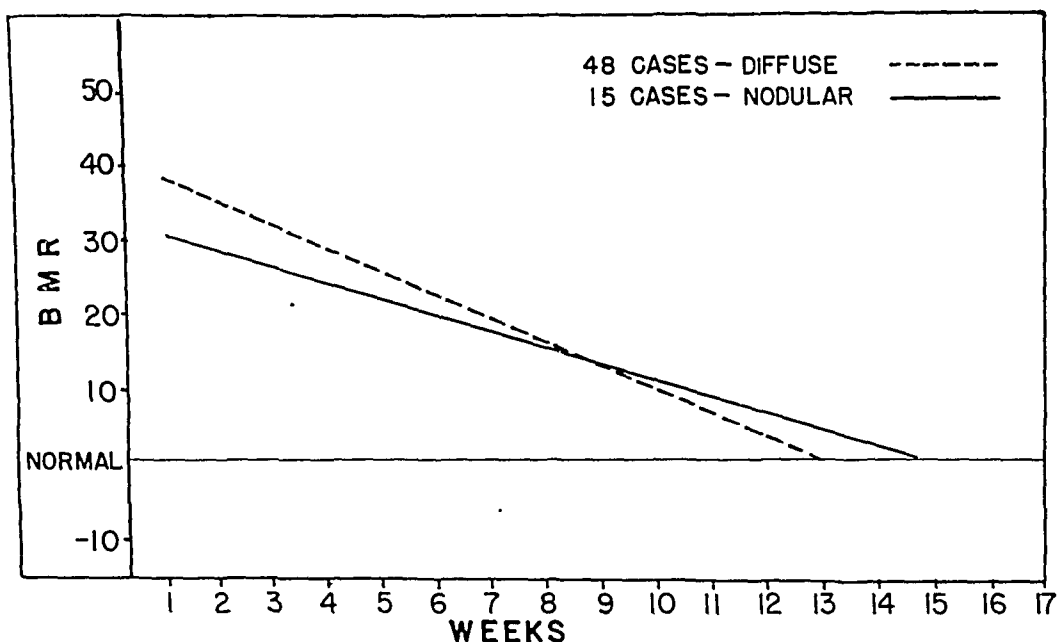
200 mg. may be tried and the dose increased if an effective response fails to occur. In this way time would be lost, but the minimum amount of the drug would be used.

With regard to speed of control a few general statements may be made. Hyperthyroidism in association with small diffuse goiters in cases in which no previous iodine has been given, react the most

of the same type as those in whom more than one recurrence may occur following operation. Such resistance to treatment certainly does not encourage hope for a permanent medical cure.

Hyperthyroidism of long standing has, in most instances in our hands, been more resistant to therapy. The goiter is usually larger under such circumstances, and perhaps the mass of reacting thyroid tissue

## AVERAGE RESPONSE TO PROPYL THIOURACIL IN DIFFUSE AND NODULAR GOITER



Average fall in BMR per week --- Diffuse goiter 2.66% - Nodular goiter 2.37%.

The average response differs little in diffuse and nodular goiters.

The very rapid responses tend to occur in the diffuse.

The very slow responses of many months occur chiefly in large nodular goiters.

CHART 1

rapidly to propylthiouracil. These promise for this reason to be among those which will respond eventually with a permanent medical cure. Instances have been seen, however, especially in young people, in which increased dosage of the drug is associated with only partial control, appearing to indicate a natural ingravescence of the disease. In some of these the thyroid continues to enlarge during treatment. These patients appear to us to be

present is a factor of some importance. We are inclined to believe that it is.

Large adenomatous goiters respond more slowly in some instances. If groups of cases are compared, however, it is interesting to note that there is only a small average difference. The impression that the opposite is the case apparently arises chiefly from the fact that there are some very rapid responses among the patients with diffuse goiter and a few very

slow responses among those with nodular goiter. Chart 1, showing average response in diffuse and in nodular goiter, illustrates this point.

A woman with acromegaly was the only patient with hypermetabolism which we judged to be at least partly of thyroid origin who has not responded at all to propylthiouracil. She has had as much as 600 mg. per day for more than 9 months.

majority it remains approximately the same or there is a slight increase, in a few there is an increase which occasionally may be extreme. The rate of increase in exophthalmos and its degree of severity appear to bear little or no relationship to the activity of the thyroid gland. In most of our patients an attempt has been made to follow the course of exophthalmos and associated eye signs by repeated

TABLE 3.—DEGREE OF EXOPHTHALMOS BEFORE AND AFTER TREATMENT

	Degree of exophthalmos				Duration of treatment weeks	B.M.R	
	Before treatment		After treatment			First	Last
	<i>O.D.</i>	<i>O.S.</i>	<i>O.D.</i>	<i>O.S.</i>			
Men . . . . .	21	22	22	22	37	+44	-18
	30	27	30	27	46	+40	- 5
	21	21	26	24	37	+62	- 9
	23	23	22	22	43	+24	+15
	21	21	25	23	28	+15	- 1
	19	19	27	28	14	+53	+ 5
Women . . . . .	19	19	19	19	48	+29	+11
	21	21	20	20	57	+28	+ 9
	25	25	25	24	59	+16	- 5
	26	24	28	27	48	+61	+10
	26	25	26	26	37	+28	+ 0
	21	20	21	20	27	+52	- 5

Little of value can be said from our data regarding the probable frequency of permanent cure of hyperthyroidism following withdrawal of propylthiouracil. The drug has been discontinued in only 17 patients. Recurrence has been noted in 6 of these. In 4 of the 6 the basal metabolic rate was never shown to have fallen to zero, and in 1 of these the drug was stopped inadvertently by the patient when the basal metabolic rate was +15%. In this instance there was more accurately an ingravescence than a recurrence.

In 2 patients, after treatment for 36 and 51 weeks, respectively, there was a recurrence in 12 weeks and in 4 weeks after cessation of medication, the basal metabolic rate to cessation being -9 and -15%, respectively. In 11 other patients remission continued for periods ranging from 1 to 30 weeks in 10 and up to 14 months in 1.

*Exophthalmos.* Exophthalmos appears to behave during treatment with propylthiouracil in much the same way as it does after thyroidectomy; namely, in the

estimation of the severity of the changes and by actual measurement of the proptosis by means of a Hertel exophthalmometer. Measurements of the proptosis have been made in each instance by Dr. A. D. Ruedemann or Dr. R. J. Kennedy. The following table (Table 3) represents measurement of the degree of exophthalmos in millimeters in a group of 12 patients in whom 3 or more measurements were made over a period varying between 14 and 59 weeks. The A.P. position of the globe is given at the beginning and at the end of this course of therapy and is stated in millimeters, and concurrent fall in basal metabolic rate is shown.

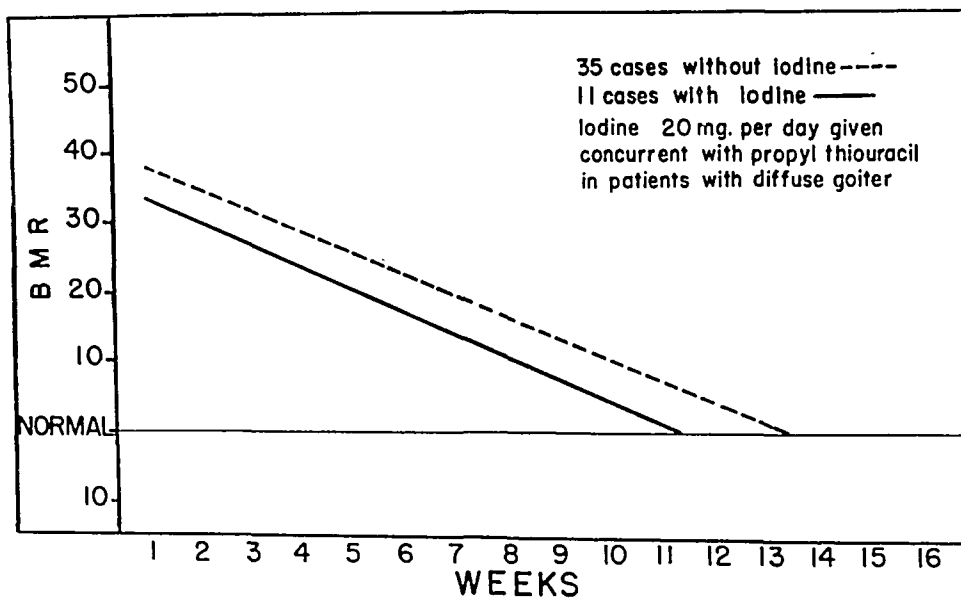
*Iodine and Propylthiouracil Given Concurrently.* Early in the use of thiouracil desiccated thyroid was used in doses as high as 2 gr. per day in the 3 patients in whom it was tried but failed to eliminate the thrill and bruit from a vascular goiter over a period of a month. Iodine, however, in doses of 10 mg. per day did so in less than a week. It became a matter of interest to know whether such manage-

ment hindered or helped the antithyroid effect as a whole or interfered with propylthiouracil later. A group of patients who had diffuse goiters of approximately the same size was chosen. Some of these were given iodine in doses of 10 to 30 mg. per day concurrently with propylthiouracil. The remainder were given no iodine. There was no significant difference in their rate of response. The following chart (Chart 2) depicts the average rate of fall

shown that the thyroid glands of thiourea-treated rats fail to take up iodine in the normal manner,<sup>4</sup> and also because experience has shown that thiouracil effect may be slowed by pre-treatment with large doses of iodine.

The proper rôle of propylthiouracil in the management of hyperthyroidism has not been settled and cannot well be settled until the matter of the control of increase of the disease during therapy and

## COMPARISON OF AVERAGE RESPONSE TO PROPYLTHIOURACIL WITHOUT IODINE AND WITH IODINE



Average fall BMR per week—without iodine 2.95% --with iodine 3.07%.

Iodine 10 mg. per day quickly eradicates the thrill and bruit which may appear.

In these doses the effectiveness of propyl thiouracil is not hindered.

Pretreatment with iodine should not be suddenly stopped.

CHART 2

of the basal metabolism in the two groups. For this reason it has become our practice to give iodine in doses of 10 to 30 mg. per day in cases of Graves' disease to prevent these signs of vascularity within the gland. It is possible that larger doses of iodine might be used concurrently with propylthiouracil treatment to produce a more rapid response without interference with the final propylthiouracil effect. In view of experimental work bearing on this phase of the problem it must be approached with caution since it has been

especially the production of lasting remissions after cessation of therapy has been adequately established.

At present our procedure is as follows, the patients having been graded into the following 4 classes:

1. In patients with small goiters and relatively mild hyperthyroidism an attempt at a medical cure is made. The aim here is to control the symptoms completely and if possible to hold the basal metabolic rate at or below zero for 8 or more months. Exception to this manage-

ment may arise for various reasons including: (1) the patient's preference for the relative certainty of a surgical cure, (2) lack of intelligence and coöperation of the patient, (3) interference of toxic effects, (4) existence of a solitary adenoma and indication for surgical removal, (5) presence of pregnancy with consideration of surgery as the more prudent course until safety of the drug to the infant is fully established.

If after adequate trial and withdrawal of the drug recrudescence is evident, a choice between its continued use and surgery must be made.

2. In all young people with hyperthyroidism of mild or moderate degree when there is no apparent risk to surgery and when thyroidectomy is decided upon, iodine preparation without propylthiouracil is usually the preoperative treatment of choice because the response is quicker. Propylthiouracil may be used but is unnecessary.

3. Complete control of the disease with propylthiouracil is advised in all patients with severe hyperthyroidism, in all those over 45 years of age, as well as in those with complicating factors such as poor cardiac status. When the disease is thus controlled Lugol's solution is given for 2 to 3 weeks in doses of 1 cc. 3 times a day. During the week preceding operation no propylthiouracil is given and thyroidectomy is performed.

4. In patients whose hyperthyroidism is complicated by extreme old age, by cardiac or other complications which will prevent their ever becoming good surgical risks even after the elimination of hyperthyroidism, propylthiouracil may be con-

tinued indefinitely. To this group may also be added those patients with post-operative recurrence of hyperthyroidism because in them the increased morbidity from nerve or parathyroid gland injuries warrants withholding further operation unless it becomes imperative.

**Conclusions.** 1. Propylthiouracil is a safe drug. In 218 patients treated for an average of 8 months and in some as long as 14 months, no cases of agranulocytosis were seen. Three minor reactions occurred, and 4 other reactions required the cessation of treatment.

2. It is effective in controlling hyperthyroidism of all types except possible instances of acute crisis in which its action is too slow. The hyperthyroidism of acromegaly may also be an exception.

3. An effective dose in more than 95% of our patients has been 300 mg. per day. A smaller dose is effective in many. A larger dose has been required in less than 4%.

4. Iodine in doses as high as 30 mg. per day may be used concurrently with propylthiouracil. It will eliminate the thrill and bruit in diffuse glands and does not hinder the action of propylthiouracil.

5. A tentative plan is presented for the use of propylthiouracil to the best advantage of the patient with hyperthyroidism.

6. The probable frequency of permanent remissions of hyperthyroidism following the use of propylthiouracil cannot yet be properly estimated. At present long-continued use of the drug appears warranted in some patients and may later appear feasible and perhaps desirable in many.

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## USE OF PYRIBENZAMINE IN PREVENTION OF HISTAMINE-INDUCED GASTRIC ACIDITY AND HEADACHE AND IN TREATMENT OF HYPERSENSITIVENESS TO COLD\*

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PYRIBENZAMINE† is one of a series of compounds the ability of which to antagonize the effects of histamine recently has been investigated by Mayer, Hutterer and Scholz.<sup>5</sup> The chemical name is N'-pyridyl-N'-benzyl-N-dimethyl-ethylene diamine hydrochloride. The drug is a white, crystalline, stable non-hygroscopic compound, soluble in water at room temperature to the extent of 130 gm. per 100 cc.

According to the aforementioned investigators, pyribenzamine in very small doses is capable of preventing the action of histamine on an isolated strip of intestine of the guinea pig. It also has anti-acetylcholine activity, but for such purpose, a dose 100 times that necessary for anti-histamine action is required. The authors named also have demonstrated that pyribenzamine is effective in delaying occurrence of the asthma which exposure to a histamine-aerosol-air stream usually produces in guinea pigs. Under ordinary circumstances, asthma appears in 35 to 90 seconds and convulsions in 1½ to 3½ minutes after exposure to histamine-aerosol-air stream. The convulsions are delayed from 2 to 6 hours if pyribenzamine is administered subcutaneously in the amount of 0.1 mg. per kilo. of body weight 15 minutes prior to exposure. According to Mayer,<sup>4</sup> the drug also protects dogs and guinea pigs against shock doses of anaphylactic substances to which the animals have been sensitized.

The mechanism of the action of pyribenzamine and other antihistamine compounds is unknown.

**FAILURE OF PYRIBENZAMINE USUALLY TO PREVENT THE INCREASE IN GASTRIC ACIDITY INDUCED BY HISTAMINE.** Fourteen persons were used in the study. Twenty-seven gastric analyses were done. The patients studied had multiple sclerosis, Ménière's disease, nerve deafness or tension headaches. A normal person also was studied. None had symptoms referable to the gastro-intestinal tract.

*Procedure.* The volume, free acidity and total acidity of the gastric content were determined. The subject was then given 0.05 mg. of histamine base intravenously. The solution of histamine diphosphate used contained 0.1 mg. of histamine base per cubic centimeter. Samples of gastric juice were then obtained every ten minutes over a period of approximately one and a half hours or until the values returned to fasting level.

Pyribenzamine was then given for a specified period of time. Dosage of the drug varied from 50 mg. twice daily to 100 mg. four times daily. The period over which it was administered varied from one to eight days, the last dose being given the day of the second test in most instances. Fasting levels of volume and free and total acidity were again determined. Then intravenous injection of 0.05 mg. of histamine base was given for the second time and analysis of gastric content was repeated in the same manner as previously described.

*Results.* Gastric acidity was increased after the 1st injection of histamine in 12 of the 14 cases. In 2 cases histamine failed to cause increased acidity. Of the 12 cases in which increased acidity was

\* Abridgment of a portion of thesis to be submitted by Dr. Perry to the Graduate School of the University of Minnesota, in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

† Ciba Pharmaceutical Products, Inc.



found after the 1st injection of histamine, in all but one acidity was increased after a 2nd injection of histamine given subsequent to the use of pyribenzamine. In 2 cases (one illustrated in Fig. 1) a less pronounced rise occurred after use of pyribenzamine, in 4 cases essentially the same results as in the initial observations were secured and in 4 cases (one illustrated in Fig. 2) an increase in acidity was found.

The foregoing determinations were not made on one person after use of pyribenzamine because the occurrence of severe side reactions, including dizziness and numbness of the hands, necessitated discontinuance of administration of the drug. Of the 2 persons whose acidity failed to increase after the 1st injection of histamine, 1 responded and 1 failed to respond to injection of histamine after the

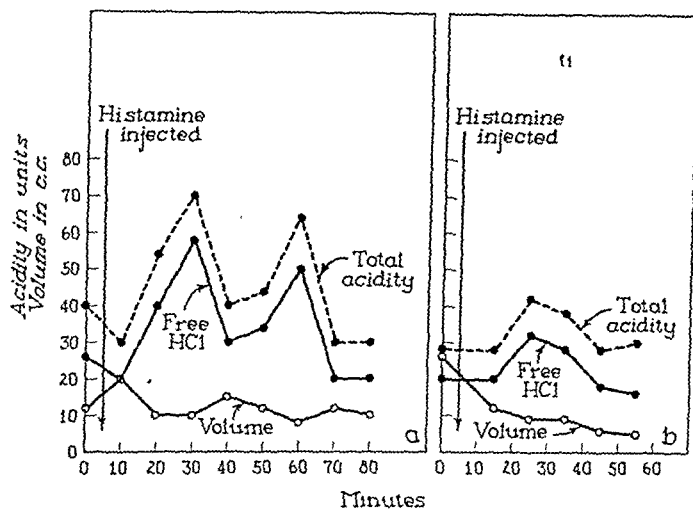


FIG. 1.—Alterations in volume and acidity of gastric contents in a case of nerve deafness: (a) after intravenous administration of 0.05 mg. of histamine base; (b) after treatment with 1600 mg. of pyribenzamine followed by intravenous administration of 0.05 mg. of histamine base.

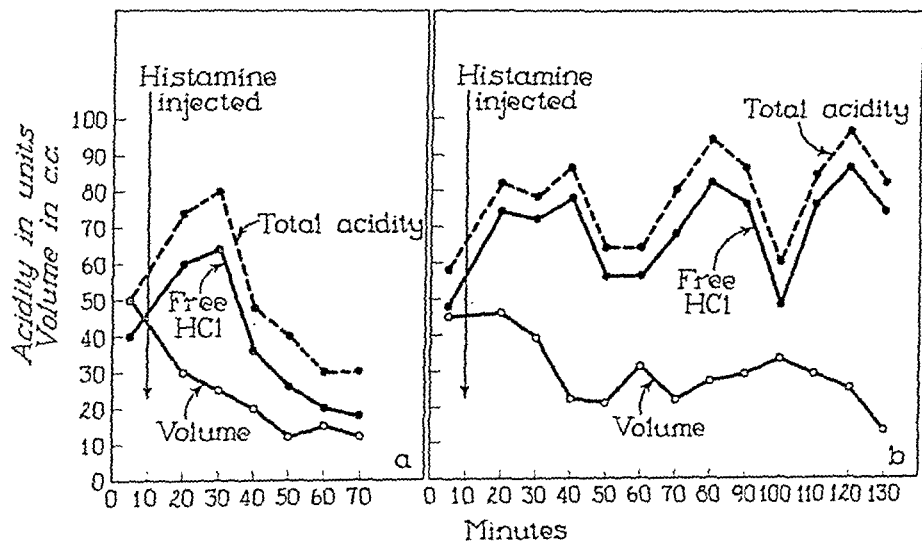


FIG. 2.—Alterations in volume and acidity of gastric contents in a case of multiple sclerosis: (a) after intravenous administration of 0.05 mg. of histamine base; (b) after treatment with 1000 mg. of pyribenzamine followed by intravenous administration of 0.05 mg. of histamine base.

use of pyribenzamine. Average values for the preceding determinations for 13 persons are shown in Table 1.

**Comment.** We cannot explain the foregoing results. McElin and one of us<sup>3</sup> (Horton) previously found in similar tests that benadryl similarly did not have a consistent effect in preventing an increase of gastric acidity after administration of histamine. Recently it has also been demonstrated<sup>7</sup> that neither benadryl nor pyribenzamine has the ability to antagonize histamine-stimulated gastric secretion in the dog.

that the 5th cranial nerve and upper cervical nerves were the afferent pathways for the conduction of pain stimuli from the intracranial vessels or surrounding structures.

**Material and Procedure.** Four student nurses volunteered as subjects for our observations of the effect of pyribenzamine in preventing headache induced by intravenous administration of histamine.

Determinations of basal blood pressure were obtained with the subjects supine. Then 0.5 cc. of a solution of histamine diphosphate containing 0.1 mg. of histamine

TABLE 1.—FAILURE OF PYRIBENZAMINE USUALLY TO NULLIFY HISTAMINE EFFECT ON GASTRIC SECRETION

	Effect of histamine only		Effect of histamine when preceded by pyribenzamine	
	Before histamine	After histamine	After pyribenzamine only	After pyribenzamine plus histamine
Gastric secretion				
Volume in cc. . . . .	33	..	27	..
Free acidity, units . . . . .	38	56	41	64
Total acidity, units . . . . .	49	69	53	76
Increase in free acidity, units . . . . .	..	18	..	23

**THE EFFECT OF PYRIBENZAMINE ON HISTAMINE-INDUCED HEADACHE.** Pickering<sup>6</sup> studied the effects of histamine in producing headache experimentally. Actual headache, he found, is preceded by flushing of the face, a throbbing sensation in the head and a fall in systemic blood pressure. The pressure of cerebrospinal fluid was observed by Pickering to increase markedly as the blood pressure decreased. In his work, headache usually came on in about 60 seconds after administration of histamine concomitant with return of the blood pressure to normal or above and with fall of cerebrospinal fluid pressure toward normal. Clark, Hough, and Wolff<sup>2</sup> made similar observations. They thought that the cause of the headache was increased dilatation of the intracranial vessels which resulted in production of painful impulses while the vessels were under normal or increased vascular tension. Schumacher, Ray and Wolff<sup>8</sup> in later studies concluded that extracranial and dural vessels play a minor rôle in the production of experimental histamine-induced headache, and

base per cubic centimeter was injected intravenously. Thereafter blood pressure was determined frequently and the subject was instructed to indicate the exact time of onset of headache, its location and severity and any changes that occurred. Following cessation of headache, pyribenzamine was administered intravenously in the following amounts: in 2 instances, 25 mg. of pyribenzamine in 100 cc. of physiologic saline solution, in the 3rd instance, 25 mg. in 150 cc. and in the 4th instance, 12.5 mg. in 100 cc. were administered. Then another intravenous injection of histamine in the same amounts as previously used was given and the observation repeated.

**Results.** In 3 of the 4 instances, the headache caused by injection of histamine was much less intense and of shorter duration after administration of pyribenzamine than before (Fig. 3). In the 4th instance headache did not develop and a decrease in blood pressure was not observed after injection of histamine. In all 4 instances there was also a definite decrease in flushing of the face and throbbing sensation in the head when the injection of histamine followed administra-

tion of pyribenzamine. As a control study, we observed that after a subject had completely recovered from headache induced by intravenous administration of 0.5 cc. of histamine diphosphate containing 0.05 mg. histamine base a similar or even worse headache could be induced by injecting again the same amount of histamine intravenously.

The woman was seen at the clinic in August, 1941, when desensitization to histamine was started. It was estimated that at the end of 16 days the patient showed about 65% improvement as measured by the amount of swelling which occurred after immersion of the hand in water at 10° C. for 7 minutes.

When the patient was again seen at the clinic, in 1946, she complained of inability

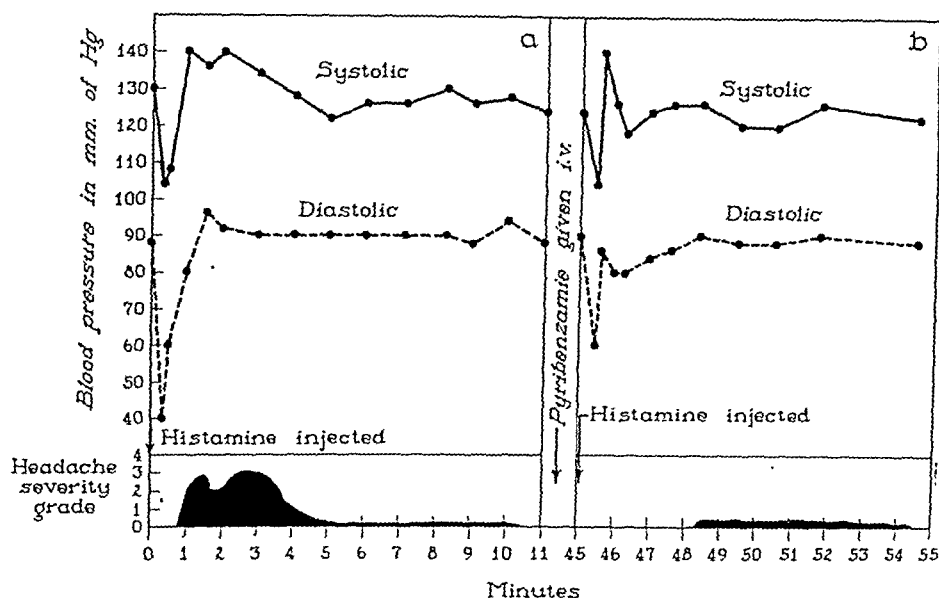


FIG. 3.—Changes in blood pressure and in severity of headache of a normal person: (a) induced by intravenous administration of 0.05 mg. of histamine base; (b) induced by intravenous administration of 0.05 mg. of histamine base after intravenous injection of 25 mg. of pyribenzamine in 100 cc. of physiologic saline solution.

**Comment.** Presumably pyribenzamine prevents the action of histamine on the cerebral vessels. Three of the 4 subjects experienced moderately severe side reactions consisting of dizziness, nausea, weakness and a feeling of pressure in the head.

#### EFFECT OF PYRIBENZAMINE IN TREATMENT OF PATIENTS WHO ARE HYPERSENSITIVE TO COLD.

**Case Reports.** *Case 1.* A white woman, aged 19 years, had first exhibited hypersensitivity to cold in 1941. She had gone swimming on May 30 and again on July 4. On the latter date, after she had been in the water about 2 minutes she became dizzy and fainted. When she was taken from the water, her body was red and edematous and her breathing was difficult. Some edema had persisted for about 42 hours.

to eat cold foods or to breathe cold air without occurrence of a sense of constriction in the throat. A rash would develop after exposure to extreme cold. Headache would also occur after exposure to cold.

A wheal was not produced by the application of an ice cube to the dorsum of the forearm for 3 minutes. However, the patient reported a sense of constriction in the throat and a headache after ingestion of ice water. Symptoms would appear in 2 to 3 minutes and would persist for 10 to 12 minutes. Benadryl administered in amounts of 50 mg. four times daily gave approximately 75% relief of symptoms. Pyribenzamine administered in the same dosage gave about 25% relief. Larger doses of the latter drug were tried but had to be discontinued because of the occurrence of a severe headache as a side reaction.

*Case 2.* A white man, aged 35 years, had had swelling of the face and hands after exposure to cold during the previous 5 years.

A wheal and a flare were produced by application of an ice cube for 3 minutes to the ventral surface of the left forearm. Immersion of the hand and forearm in water at 10° C. for 12 minutes resulted in edema of the hand, including the fingers. The edema, which extended up to the line of immersion, persisted about 7 hours. Pyribenzamine was given, 150 mg. at night and 150 mg. the following morning, after which the afore-mentioned tests were repeated. A wheal was not produced by application of an ice cube to the ventral surface of the forearm; however, edema of the hand and forearm occurred after immersion for 12 minutes in water at 10° C. The patient was then given another dose of 150 mg. of pyribenzamine. The edema in this case lasted for only an hour.

*Case 3.* A student nurse, 20 years of age, had urticaria after exposure to cold air. She was observed on one occasion after she had been exposed to cold air for a few minutes and urticaria had developed on the arms, forearms and thighs. The urticaria was accompanied by itching. A dose of 15 mg. of pyribenzamine in 100 cc. of physiologic saline solution was administered intravenously at the rate of 12 drops per minute. The pruritus ceased in 3 minutes and the urticarial wheals disappeared in approximately 10 minutes. The drug apparently had no effect on swelling of the lip which had appeared concomitantly with the urticaria. The patient became drowsy during administration of pyribenzamine.

She subsequently took the drug orally with prophylactic or therapeutic intent; she found that urticaria would not develop after prophylactic use of the drug and that pruritus and urticaria, once they had begun to develop, would disappear after therapeutic use of the drug. Two weeks after she had made the foregoing observations she reported that the drug seemed to have lost some of its effectiveness and that she then required 100 mg. to produce the same benefit as 50 mg. had given previously. This patient also tried the effect of benadryl and found that it took 100 mg. of benadryl to produce the same effect as 50 mg. of pyribenzamine.

Arbesman, Koepf and Lenzner,<sup>1</sup> in a clinical report on the use of pyribenzamine, found it effective in preventing the wheal response to application of an ice cube in cases of physical allergy to cold, as well as in enabling patients to tolerate cold without discomfort.

**Comment.** We should point out that in our Case 1 the manifestations were entirely subjective. In Case 2 the edema persisted for only about an hour after administration of pyribenzamine as compared with a duration of 7 hours when the drug had not been used. Urticaria, which was the manifestation in Case 3, disappeared shortly after administration of pyribenzamine. Both benadryl and pyribenzamine were used in 2 of the cases under discussion. One of the 2 patients derived greater symptomatic relief from benadryl while the other showed greater response to pyribenzamine when the drugs were given in the same dosage.

**Summary and Comment.** Pyribenzamine, a new antihistamine compound, has been studied with respect to its effectiveness in preventing the rise in gastric acidity induced by administration of histamine, in prevention of headache initiated by intravenous injection of histamine, and in respect to its effect on the symptoms and signs of hypersensitiveness to cold exhibited by 3 patients.

There was no consistent effect of the drug in preventing the increase of gastric acidity induced by administration of histamine. The amount of pyribenzamine used in these cases varied from 100 to 400 mg. daily given in divided doses and the drug was administered over periods varying from 1 to 8 days.

Headache induced by intravenous injection of 0.05 mg. histamine base was almost entirely prevented by intravenous administration of 12.5 to 25 mg. of pyribenzamine. Because of side reactions, we do not recommend that it be administered intravenously. We did not, however, observe any acute hypotension or other alarming reactions following intravenous use of the compound.

Three patients who had symptoms or signs of hypersensitiveness to cold were studied. Pyribenzamine was of some value in all 3 cases in reducing the severity or duration of symptoms caused by application of provocative measures. In the one case in which, on adequate trial, pyribenzamine was found to be of value

in preventing or aborting urticaria induced by exposure to cold, it was necessary, after a period of 2 weeks, to increase the dose of drug used. It should be emphasized that it is not a cure for hypersensitivity to cold but that it may give symptomatic relief and deserves further study in this condition.

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### APPLICATION OF IMMUNOLOGIC PRINCIPLES TO THE MANAGEMENT OF HAY FEVER, INCLUDING A PRELIMINARY REPORT ON THE USE OF FREUND'S ADJUVANT

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ANIMALS exposed to infection produce in their blood and tissue fluids soluble substances which tend to prevent or cure infection. These are called antibodies since they act against the foreign agent and often confer protection or immunity against it. Antibodies do not always, however, confer increased resistance but may actually raise the susceptibility (or cause sensitization) of the host. This was shown nearly 50 years ago when Portier and Richet<sup>39</sup> reported that toxic extracts of the sea anemone's tentacles were tolerated by dogs in a first injection but produced violent, and often fatal, responses when reinjection was carried out some days later. To characterize this lowering of resistance, they coined the phrase "anaphylactic action" to distinguish it from its antithesis, the prophylactic or protective response. Another, and perhaps similar, type of increased susceptibility is to be seen in allergic individuals who develop, for some unknown reason related to heredity, antibodies which sen-

sitize them to ordinarily harmless pollens. It is with this class of "pseudo-defense" reaction that the present article will deal.

*Historically*, the first clue to the immunologic nature of hay fever was given by the discovery of a related antigen, or foreign substance giving rise to the formation of antibodies. Although seasonal "catarrh" had been blamed upon solar light, the heat of summer, bacteria, the gouty diathesis, ozone and the emanations of flowers and plants, it was Blackley<sup>3</sup> who first gave scientific evidence that the last-named factor was the real cause. He not only reproduced the sneezing attacks in himself by exposure to pollen but also showed that susceptible patients reacted violently to pollen placed on the nasal, buccal or ophthalmic membranes or on the abraded skin. Thus a specific agent was shown to produce a susceptibility later called hay fever.

Despite these excellent contributions, Blackley had few followers during the next 30 years, therapy in hay fever being

directed toward the correction of "local pathology" in the nose by means of surgery, or electrocautery. In 1903 Dunbar<sup>10</sup> revived the pollen theory and, in an effort to duplicate the success of antitoxin in diphtheria, applied the serum of pollen-inoculated animals to the inflamed membranes of allergic subjects. Although the considerable efficacy of this therapy strengthened the concept that the disorder was related to a specific antigen, final conviction awaited the demonstration by Noon<sup>38</sup> in 1911 that it could be prevented by a series of preseasonal injections with pollen extract. The concept at this time was that hay fever was the result of a combination of antigen with an antibody probably of the same type as that demonstrated in sensitized animals. Since it had been shown that anaphylaxis could be prevented by means of repeated small injections during the interval between the first and the later "shocking" dose, the success of Noon's therapy was explained on a similar basis and his procedure referred to as "desensitization." It made the assumption that the hypothetical antibodies of hay fever were gradually saturated and inactivated by the administered antigen.

Ten years later, evidence for the existence of allergic antibodies was first given by Prausnitz<sup>40</sup> when he injected a small amount of serum from fish-sensitive Kuestner into normal skin and obtained an urticarial response to a later test with the fish extract. Although this demonstration added to the theory that hay fever and other allergic disorders were analogous to anaphylaxis in that the antigen-antibody reaction was detrimental to the host, it was not long before certain differences in the 2 states were pointed out. For example, the quality of the experimental antibodies to precipitate and to fix complement when mixed with their antigens could not be shown for the Prausnitz-Kuestner factor. The susceptibility of the latter to heating also stood in contrast to the other antibodies. By 1926 Levine and Coca<sup>25</sup> threw more doubt

on the theory by showing, in PK (Prausnitz-Kuestner) experiments with serum from hay fever cases, that allergic sensitizing bodies were not decreased but were often increased in the circulation as the result of Noon therapy. Thus the phenomenon of desensitization, so characteristic of the experimental state, was not to be elicited in man. Schmidt and Lip-pard<sup>41</sup> later tried to reconcile the 2 schools by suggesting that the very increase in allergic antibodies might serve to bind up the antigen in the blood stream before it could reach the allergic tissues and cause distress. However, this theory is not convincing when one considers that atmospheric pollen contacts the eyes and nose *before* gaining entrance to the circulation. Although there was uncontested acceptance of the idea that hay fever was due to the union of allergic antibodies (or reagins, as Coca preferred to call them) with pollen antigen in the tissues, the mechanism underlying Noon's prevention of symptoms was unknown for years after the Prausnitz-Kuestner demonstration. Indeed, many allergists claim that it is still a mystery.

There were clues to a possible answer, however, in the European literature of the late 20's and early 30's. Van Leeuwen and Kremer<sup>46</sup> noted that serum from some mold-sensitive cases tended to reduce the response of skin allergic to this antigen. The following year, Jadassohn<sup>22</sup> described a similar neutralizing quality in ascaris-sensitive serum. It is of interest that both these observers believed that the sensitizing and neutralizing functions of their sera were properties of 1, rather than of 2, immune bodies. Shortly György, Moro and Witebsky<sup>16</sup> distinguished, however, between egg-allergic and egg-immune infants by means of the different zones of complement fixation shown by their sera, and Woringer<sup>49</sup> too referred to "*deux sortes d'anticorps ovalbuminiques*" in the blood of nurslings.

In 1935 Cooke, Barnard, Hehald and Stull<sup>7</sup> stimulated interest in the concept of 2 coexisting types of antibody by

observing that the neutralizing quality was to be found only in sera of those of their hay fever patients who had been receiving *treatment* of the Noon variety. After a number of injections, a reduction could be found in the whealing that resulted when the patient's serum was mixed with antigen and introduced into normal skin. To explain this reduction they postulated the development, during pollen therapy of hay fever patients, of an immune factor differing from reagin (or Prausnitz-Kuestner antibody). Because this interference with whealing was noted in serum-antigen mixtures when tested in normal skin but not when injected into allergic skin, they concluded that the phenomenon was not due to combination of antigen with the new factor but to some other undetermined process. Because an antibody by definition must react demonstrably with its antigen, they referred to the hypothetical substance as a "peculiar, blocking or inhibiting type of immune antibody." Although Harley<sup>20</sup> concurred that the Cooke factor did not bind its antigen, it was later shown by the author<sup>26</sup> that the substance was an antibody and that the failure of earlier investigators to detect its antigen-binding nature was referable to their use of excessive amounts of antigen.

Within the next 2 years, the author<sup>8</sup> experimenting in Cooke's laboratory, succeeded in producing pollen antibodies in three normal volunteers. These antisera possessed the blocking principle described by Cooke but lacked all sensitizing power; that is, gave negative PK tests. At the same time, Cohen and Nelson<sup>5</sup> were independently producing the same immune body in normal sheep by means of pollen injections. Although it was natural to assume that such an antibody was formed by hay fever subjects, it was not until 2 years later that a means was found to separate it from the coexisting reagins which had confused the results of PK tests. By means of controlled heating, the writer<sup>26</sup> inactivated the reagin present

in the serum of treated, pollen-sensitive patients and then titrated the still active immune antibody. It was thereafter a simple matter to compare the antigen-combining quality of such heated sera with that of specimens taken from the immunized, non-allergic volunteers. No difference could be detected between the two.

The newly found antibody was formed with regularity in all subjects, whether allergic to the antigen or not. It bound and inactivated its pollen antigen, as demonstrated by negative urticarial responses to pollen-serum mixtures tested in naturally sensitive as well as in passively sensitized skin. This neutralizing capacity was definite but limited, the usual skin-test reaction resulting if too much antigen was introduced into the test mixture. The antibody differed from reagins not only in its resistance to heat and in its failure to sensitize skin but also in the speed with which it disappeared from inoculated cutaneous sites. This latter characteristic had been touched upon by Langner and Kern<sup>24</sup> in their earlier experiments with unheated, post-treatment serum from pollinosis cases.

Adequate confirmation has been made of the existence of these immune bodies. Sherman, Hampton and Cooke<sup>43</sup> found that such heat-resistant antibodies were transmitted to the offspring through the cord blood whereas the reaginic bodies of the mother were unable to pass the placental barrier. Gelfand and Frank<sup>15</sup> noted the induced antibodies in their treated hay fever subjects with regularity, as did also Maunsell.<sup>37</sup> Whereas these investigators employed modifications of the passive transfer technique employed by the writer,<sup>26</sup> Scully and Rackemann<sup>42</sup> arrived at the same conclusion by the use of the older method of Cooke wherein not only the thermostable factor but also the unheated reaginic components of the serum contribute to the end-points.

Recently another procedure for measuring thermostable antibodies in human serum has been suggested by Hampton, Johnson, Alexander and Wilson.<sup>19</sup> This



microprecipitin technique calls for the use of rabbit antipollen serum. The extent to which the precipitation of rabbit serum can be postponed by the presence of human thermostable antibodies serves as a measure of the latter. Presumably, the method indicates the amount of antigen which is bound and neutralized by the human serum. As in the instance of the passive sensitization type of titration, there appears to be a successful competition by the thermostable antibody for the antigen which is thereby prevented from uniting with the rabbit antibodies. In several reports, evidence for the presence of the neutralizing, heat-stable antibodies in the treated ragweed-sensitive patients has been given by this method.<sup>1,2</sup>

Although Cohen and Weller<sup>6</sup> believed that they could distinguish post-treatment serum from that of the untreated patient, Swineford<sup>45</sup> has not been able to substantiate their claims using the same, collodion particle method of agglutination.

The existence of these 2 different types of antibody in man has, however, been observed by workers investigating other antigens. Lowell<sup>35,36</sup> deduced that antibodies similar to pollen-reagins accounted for his patient's urticaria, bronchial constriction and collapse after taking insulin, whereas thermostable, neutralizing factors were responsible for her periods of insulin-fastness. Similar antibodies have been found by the author<sup>32</sup> in a woman who was exquisitely allergic to insulin. As graduated doses of insulin gradually built up a high level of clinical tolerance, her blood and tissues gave evidence of acquiring neutralizing antibodies which proved to be heat-resistant. When therapy was interrupted, this immunity was lost and a small dose of insulin led to extreme urticarial eruption and collapse. Her reagins remained relatively unchanged throughout the period of study. In addition to insulin, a number of other antigens have been noted by us to produce the 2 varieties of immune response. Among these are crystalline ovalbumen, bovine

lactalbumen, beef and lamb, silk, and animal danders.

That this dual antibody relationship is not confined to man has been brought out by Wittich<sup>48</sup> in the case of dogs and by Weil and Reddin<sup>47</sup> for cattle. Whereas their animals showed spontaneous pollen allergy, numerous other workers have been able to induce the 2 varieties of immune body in rabbits and guinea pigs.

*The clinical rôle of thermostable antibodies in man* has proven a most difficult matter to determine, in spite of the strong logic in the idea that a factor capable of neutralizing a foreign irritant should be of protective value to its host. At the outset of exploring this possibility, it was necessary to learn whether the antibodies were present in the tissue fluids as well as in the circulation; for it was not to be expected that immunity distant from the allergic portals of entry would prove of much worth in preventing hay fever. Although it was the accepted belief that successfully treated patients showed no loss of skin sensitivity, delicate threshold tests revealed that this was a misconception.<sup>27</sup> Not only in the skin but also in the conjunctiva, it could be shown that the tolerance rose or subsided as the titer of thermostable antibody in the patient's blood was increased by Noon's therapy or was allowed to fall by discontinuing the pollen injections. This relationship between circulating and fixed antibodies was confirmed by Sherman.<sup>44</sup> The assumption that the induced antibodies played some rôle in the patient's protection against the atmospheric pollen was strengthened decidedly by this finding. This assumption is, however, strongly contested as the following comments will indicate.

When the antibody was still in the hypothetical stage, the Cooke group<sup>7</sup> were enthusiastic about their success with transfusions of blood taken from treated cases of hay fever, and spoke of a "transferable protective substance." Langner and Kern<sup>24</sup> noted a similar reduction in symptoms when untreated indi-

viduals were injected intramuscularly with 50 cc. of serum drawn from immunized patients. Our own transfusions of blood or serum taken from highly immune, normal subjects who lacked the reagins present in earlier experiments proved to be promptly effective in acute hay fever.<sup>34</sup> Attempts to correlate the titer of thermostable antibody with the relative freedom from hay fever noted among groups of patients have, however, been less encouraging. Although Maunsell<sup>37</sup> related seasonal resistance to the concentration of her patient's antibody, neither Scully<sup>42</sup> nor Gelfand<sup>15</sup> have detected any such connection. Among others, Cooke<sup>9</sup> is now of the opinion that the thermostable antibodies are not the important factor in clinical immunity.

These discouraging results should not, however, lead anyone to abandon the theory of protective antibodies in allergy. There is no other reasonable explanation. It is clinically well known that the protection resulting from injections is specific. This fact requires the assumption of a specific nature of the protective mechanism. In other words, as Coca<sup>4</sup> points out, "the protective mechanism must neutralize either the sensitizing antibody or the antigen." Since the sum total of pollen antigen given during a course of treatment is sufficient to neutralize only a small fraction of the reagins and since it is well established that reagins are not diminished by therapy, the relief of hay fever cannot be attributed to desensitization. This situation leaves, to continue the quotation, "only one other conceivable explanation of the phenomenon we are discussing: namely, that it is the result of the formation of neutralizing immune antibodies."

There are, in addition to such theoretical arguments for the existence of a protective antibody in hay fever, a number of practical reasons why a correlation between antibodies and clinical control might be extremely difficult to demonstrate. For example, all investigators (except Alexander) who have attacked the problem

have limited themselves, to date, to the method of passive sensitization. These techniques are apt to produce inconstant results except after long experience. Furthermore, the end-points obtained vary decidedly with the test subject chosen, and this fact has been disregarded by everyone. Scully neglected to remove a variable from her studies when she titrated her sera in the unheated state. In contrast, Maunsell was dealing with thermostable components only when she determined the pollen-binding power of her patient's serum by means of tests in his own skin. We found this "auto-transfer" method very satisfactory some years ago.<sup>26</sup> The influence of the "test-subject" under such circumstances would not be expected to confuse the issue in the manner of a borrowed test-subject, since any host factors affecting the serologic titration would likewise probably be reflected in the clinical outcome.

Another, less important, variable in the serologic technics is the factor of ageing of the test-antigens. This has not been given adequate attention.

Far more significant than these variables are others referable to the patient himself. Neither the external environment (with reference to atmospheric pollen and many other influential factors) nor the internal environment (including the concentration of reagins, and innumerable physical and mental factors contributing to the end-result in hay fever) can be held to be alike in any 2 patients. Just as there is a range of reactions in most biologic mechanisms, such as the response to drugs, hormones like insulin, antiserum and a host of other agents, so also one would anticipate that 2 individuals with identical amounts of thermostable antibody might show somewhat different behavior during the pollinating season.

With this biologic variation in mind, we sought to reduce the complexity of the situation by concentrating on the individual rather than on groups as had been the case with other investigators seeking correlation between serologic and

clinical immunities. Among 52 patients observed for a number of years, it was found<sup>29</sup> that a tendency was present for symptoms to be milder when the blood titer was high than when it was lower.

Further simplification has been attained by replacing the serologic procedure with direct conjunctival testing of the patient. The undesired influence of the borrowed test-subject was thereby replaced by the desired effect of native host factors on the outcome of the titration. As anticipated, the level of conjunctival response which was associated with optimal clinical protection was found to vary with the individual, but these differences were not as great as those encountered in passive sensitization procedures. By thus reducing the variables in the test, it became evident, even in making comparisons among a group, that the higher conjunctival thresholds of 95 subjects were usually associated with the better clinical results.<sup>33</sup> The correlation was not sufficiently close, however, to permit of accurate predictions in advance of the season of pollination in the instance of newly acquired patients. Once the conjunctival threshold for a given individual had been determined in relation to a successful season, it could be used as a satisfactory index to future immunization. We are continuing to accumulate this type of ophthalmic and clinical data with a view to making statistical analysis of groups segregated according to underlying sensitivity. At present there is adequate population in only 1 class of sensitiveness, that of patients whose eyes respond to *small* test-doses of antigen (after they have been given a respite from injections for at least 10 months). Among 77 such equally allergic subjects, a tendency has been noted for the median hay fever hours to be progressively fewer as the conjunctival thresholds were found higher after therapy. By segregating cases in this way, it should prove possible to minimize the influence of at least 1 of the biologic variables—that of sensitizing antibodies—

and thereby to increase the significance of group studies.

When more controlled means of testing the relationship between conjunctival reactivity and clinical susceptibility are evolved, it may well be found that the tolerance of the eye reflects the general immune status of the patient with considerably more reliability than can now be claimed. The basis for this statement is our experience with the eye test as a guide to the tolerance for injected antigen. For the past 5 years, it has been our practice to give each patient as much pollen antigen as he could take at every visit. Recent comparisons between the speed of therapy and the degree of ophthalmic sensitivity noted prior to the course have revealed a relationship between the 2. Although a range of speeds has been tolerated by the various members of each eye test group, the median values reveal a steady improvement in the capacity to take antigen as the conjunctival sensitivity preceding the course is lower. By referring to a curve constructed for each conjunctival class of initial sensitiveness, it is now possible to see what proportion of patients with a given degree of allergy have tolerated different paces of immunization. It is our custom to start a new patient on that booster schedule which has been safely taken by three-quarters of the patients in his eye class. This demonstrated correlation between the conjunctival and the systemic susceptibility makes it likely that a similar connection may eventually be found to exist between the eye classification at the end of treatment and the patient's behavior toward atmospheric pollen. A testing chamber with controlled pollen atmosphere would aid in the exploration of this prospect.

The attempts of Alexander<sup>1,2</sup> to find a relationship between thermostable antibodies and clinical relief were at first fruitful and later discouraging. Some of the difficulties enumerated above for the biologic methods of titration were also present in his studies. He did, however, exclude

the test-subject variable by using the Hampton precipitin technique.

*Practical contributions to medicine* have come out of the preceding theoretical investigations on the immunology of allergy. One of these is the short, or "booster," pre-seasonal treatment. The clue to this was found during the production of pollen-neutralizing antibodies in normal volunteers.<sup>28</sup> In order to learn whether the phenomenon of the so-called anamnestic response could be elicited, the subject was allowed a period of rest for some months and then stimulated with a large dose of antigen given in a short period. When an acceleration and heightening of antibody production resulted, it was decided to apply the principle with caution to the hay fever patient. After their initial therapy and an ensuing rest period, these subjects were able to take much faster courses than at first, and produced antibody more rapidly and more vigorously.<sup>30</sup>

By utilizing this "booster" principle and limiting the seasonal dose to that amount of antigen which would raise the eye response to a level known to be associated with clinical immunity, it has been found<sup>31</sup> that most individuals need far less therapy than is customarily given. Indeed, the average patient can be given his optimal result in as few as 7 or 8 injections and with as little as 0.1 mg. of "protein" nitrogen. The safety of such intensive therapy may be insured by adjusting the rate of increase in dosage to the tolerance of the individual, as judged by initial eye test and observation of the localized responses to each injection.

This year, a means of still further curtailing the treatment of hay fever has been tried in our laboratory. It is a procedure borrowed from experimental immunologists, who for many years have sought to improve the immune responses of animals by including various adjuvant substances in their antigenic solutions. Allergists, too, have sought for synergistic effects from such substances as gelatin, alum, tannic acid precipitation of the excitant, and admixture of their allergens

with oil. Recently a very successful adjuvant procedure has been described by Freund.<sup>11,12,13</sup> This consists of emulsifying the aqueous antigen with mineral oil containing killed acid-fast bacilli and a lanolin-like substance, Falba or Aquaphor. Antibody responses to such emulsions are strikingly heightened and prolonged, even in some instances where the tubercle bacilli or acid-fast organisms are omitted. Whereas Freund employed such antigens as horse serum, typhoid bacilli and toxoid as antigens, Friedewald<sup>14</sup> had equal success in his animals with the use of influenza vaccine. Omission of the acid-fast bacilli diminished the synergistic effect. Kulka and Hirsch<sup>23</sup> noted that the incorporation of ragweed pollen extract into Aquaphor and paraffin containing killed tubercle bacilli led to high and persistent antibody production as well as to marked sensitivity in rabbits and guinea pigs. Henle and Henle<sup>21</sup> are the first to have published on the use of this adjuvant method in man. Vaccination of 80 women with influenza A and B antigens, in an emulsion of mineral oil and Falba, produced higher and more sustained titers than were found among the control group given aqueous vaccine. Halbert, Mudd and Smolens<sup>17</sup> had notable success with Shigella antigen in mineral oil and Falba, and concluded that the presence of acid-fast bacilli was not an important factor in the effectiveness of the menstruum. In additional laboratory experiments with this simplified form of the adjuvant, these investigators<sup>18</sup> were able to reduce decidedly the acute toxicity of such substances as ricin, botulinus and tetanus toxins. They have not yet published their results with the use of simplified adjuvant in 70 human subjects.

These observations have stimulated the author to test the efficacy of the simplified adjuvant mixture in pollen-allergic patients. Accordingly, 14 patients were given their booster stimuli in the form of 1 injection containing from 200 to 2000 units of ragweed antigen emulsified in Falba and mineral oil; 18 others took 600 to 7250 units in 2 such subcutaneous

treatments, a few days or weeks apart. One individual was administered his usual dose of 11,000 units in 4 visits. The volume of each injection was between 0.1 and 0.3 ml. of the emulsion.

In keeping with the reduction in toxicity noted by Halbert, there were remarkably few untoward reactions to these doses, which ranged in size from 2- to 20-fold the amount previously tolerated by the patient in aqueous form. Whereas, only 4 mild systemic responses occurred in connection with the first 33 treatments, more difficulty was encountered after the 19 second inoculations which elicited 2 slight, 1 moderate and 1 severe overdose reaction. These doses were larger than the initial ones given the same individuals by  $2\frac{1}{2}$ - to 6-fold. The limits of safety of the procedure were thus exposed. In all, 9 untoward responses were encountered among 54 adjuvant doses given our 33 subjects. All but 2 were of mild nature.

The immunologic responses to adjuvant antigen were gauged by the usual threshold tests of the conjunctiva, comparisons being drawn with similar data for past seasons when total preseasonal doses of 10,000 units or more had been administered in aqueous form. Whereas these past courses had improved the ophthalmic tolerances by ratios ranging from 1 to 32 with a median value of 4, the adjuvant courses have increased the reaction level of the eye by about twice these amounts, the range being 2 to 64 and the median ratio being 8.

The clinical efficacy of this new form of immunization can be gauged now that the current season of ragweed pollination is over. Among the 31 members of the adjuvant group whose clinical data are up to date, 13 give a history of having gained almost complete relief from their original symptoms. This figure is to be compared

with 10, the number of excellent results recorded by them in an earlier year. A loss of at least three-fourths of their hay fever has been noted by another 8 of the subjects, which is identical with the number claiming this degree of success for a prior season. Fair responses (loss of 50 to 70% of original symptoms) were reported by 5 of the series whereas 9 of them had given a similar estimate for a preceding course. Poor outcomes, with less than half of the hay fever abolished, were described by 5 of the 31 individuals. Three of these had failed to procure relief after usual therapy. Moreover, our "pollen" count was 1807 in 1947, compared to 1332 in 1946 and an 18-year mean of 1109.

On the whole, it would appear that the clinical efficacy of the abbreviated therapy in adjuvant form compares favorably with that of more protracted courses calling for aqueous antigen. There has been no localized discomfort or abscess formation, as encountered in 2 of Henle's 80 patients. The incidence of untoward reaction can doubtless be reduced during future trials.

It should be emphasized in closing that this form of adjuvant therapy is in its developmental stages and is under no circumstances ready for application to office practice. Only by virtue of our intimate acquaintance with each patient's tolerance was it justifiable to administer the amounts of antigen specified above. The investigation is mentioned because of its interesting implications for the future management of allergic diseases and particularly because of its bearing on the theory of protection. This further demonstration that an immunologic procedure can bring about a clinical insusceptibility which is associated with the production of specific, neutralizing antibodies makes the concept of a protective rôle for these bodies still more valid.

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## RADIOLOGY

UNDER THE CHARGE OF

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SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINNESOTA

## RHEUMATOID SPONDYLITIS

BY DAVID G. PUGH, M.D.

THE work of recent investigators<sup>1,2,5,6,9,12-15</sup> has greatly increased knowledge of rheumatoid spondylitis and has resulted in the establishment of criteria for the early diagnosis. The purpose of this review is to emphasize these criteria. For those who are interested in the clinical aspect of the subject the works of Polley,<sup>14</sup> Boland and Present,<sup>1</sup> Boland and Shebesta,<sup>2</sup> Polley and Slocumb,<sup>15</sup> Hench, Slocumb and Polley,<sup>9</sup> and Dunham and Kautz<sup>5</sup> are especially recommended.

The diagnosis of early rheumatoid spondylitis reflects progress in radiology since roentgenologic observations often contribute important information which may lead to the diagnosis being made before the symptoms are conspicuous and it is not infrequent that the roentgenologic diagnosis of early rheumatoid spondylitis is made before that condition has been suspected clinically. Clinicians who are especially interested in this disease can recognize it by the symptoms alone very quickly, but physicians who are not so well acquainted with it not infrequently fail to recognize the indefinite symptoms of early rheumatoid spondylitis. Therefore the roentgenologist can be of great service by recognizing the early roentgenologic manifestations of the disease and suggesting the presence of that condition to the clinician.

Confusion in terminology has led to misunderstanding with regard to rheumatoid spondylitis. There are not many types of arthritis of the spinal column. Hypertrophic arthritis or osteo-arthritis of the spinal column is not the result of infection or inflammation but merely of wear and tear. Infectious arthritis due to cer-

tain specific infections is usually localized to a few segments of the spinal column; the infections include tuberculosis, brucellosis, typhoid and pyogenic infections. Tabetic arthropathy falls in a special category. Rheumatoid spondylitis is the only other true arthritic process affecting the spinal column and it is the only one, aside from osteo-arthritis, which may affect the entire spinal column. The use of numerous synonyms has led to considerable confusion. Polley has assembled the following synonyms for rheumatoid spondylitis: (1) spondylitis ankylopoietica (Fraenkel); (2) spondylitis ossificans ligamentosa (Knaggs); (3) spondylitis rhizomelique (Marie); (4) spondylarthrititis ankylopoietica; (5) spondylitis ankyloarthritica; (6) spondylitis adolescens (Scott); (7) vertebral type of arthritis deformans (Osler); (8) spondylitis deformans (common term in England); (9) ankylosing polyarthrititis (Oppel); (10) fibrositis ankylopoietica dorsi (Krebs); (11) syndesmitis ossificans; (12) spondylitis atrophica ligamentosa; (13) Marie-Strümpell's disease; and (14) von Bechterew's disease.

Naturally the use of so many different terms has not aided in clarifying the subject. The early investigators did not have the advantage of roentgenologic observations and, therefore, their understanding of the disease was necessarily the more incomplete. This applies especially to the former belief that there were 2 types of rheumatoid spondylitis: the Marie-Strümpell type that was supposed always to begin in the lumbar region, and the von Bechterew type which was supposed to start in the thoracic region. There is

no reason to divide rheumatoid spondylitis into 2 types. According to most observers the disease almost always starts in the sacro-iliac joints and the lumbar apophyseal joints and then progresses upward. Only rarely is the thoracic portion of the spinal column involved when the sacro-iliac joints and lumbar portion are not involved also. In an endeavor to clarify the situation the American Rheumatism Association has adopted the term "rheumatoid spondylitis;" the use of that term by all investigators is most earnestly recommended.

Hench, Slocumb and Polley<sup>9</sup> have defined rheumatoid spondylitis as an inflammatory disease of unknown origin which generally begins in the sacro-iliac joints and progressively involves the apophyseal joints of the spinal column, the paravertebral muscles and ligaments and the costovertebral and costochondral junctions. Inflammation, destruction and, as a rule, ankylosis of the sacro-iliac joints occur. Synovitis with destructive arthritis of the apophyseal joints is followed by ankylosis. Painful spasms and contractions of the paravertebral muscles occur. Calcification of the paravertebral ligaments is seen. Sometimes the hips and, less often, other joints of the extremities are involved. The shoulders are affected only occasionally. Hence rheumatoid spondylitis is chiefly a disease of the spinal column or torso.

As the term "rheumatoid spondylitis" implies, this condition is thought by many to be related to rheumatoid arthritis. This relationship has not been definitely established and it is still the subject of considerable controversy. The arguments favoring and opposing this concept have been summarized by Hench, Slocumb and Polley.<sup>9</sup> In opposition to the concept are the following points: (1) The sex incidence of the 2 diseases is different. Rheumatoid arthritis is 2 or 3 times more frequent in women than in men. Rheumatoid spondylitis is 9 times more frequent in men than in women. (2) The age incidence also is different. Rheumatoid

arthritis develops most frequently in persons who are between the ages of 25 and 40 years. Rheumatoid spondylitis develops usually in persons who are between 15 and 30 years of age. (3) Calcification of ligaments is rare in rheumatoid arthritis and common in rheumatoid spondylitis. (4) Subchondral rarefaction occurs in rheumatoid arthritis whereas subchondral osteitis is seen in rheumatoid spondylitis. (5) Subcutaneous fibrous nodules are found in rheumatoid arthritis but not in rheumatoid spondylitis. (6) Iritis is 2 or 3 times more common in rheumatoid spondylitis than in rheumatoid arthritis. (7) The concentration of agglutinins of hemolytic streptococci in the blood is lower and that of plasma phosphatase is increased more often in rheumatoid spondylitis than in rheumatoid arthritis. (8) More or less complete remissions are more common in rheumatoid spondylitis than in rheumatoid arthritis. (9) Chrysotherapy is effective in a considerable percentage of the cases of rheumatoid arthritis but is of no value in rheumatoid spondylitis. (10) Roentgen therapy is of value in rheumatoid spondylitis but is not useful in the treatment of rheumatoid arthritis.

Favoring the concept that rheumatoid spondylitis is the spinal equivalent of rheumatoid arthritis are the following points: (1) In cases of rheumatoid spondylitis arthritis of peripheral joints sometimes develops which is clinically indistinguishable from peripheral rheumatoid arthritis without spondylitis. (2) The pathologic reactions in the affected hips and peripheral joints of rheumatoid spondylitis are identical with those of rheumatoid arthritis without spondylitis. (3) In certain cases in which peripheral joints are affected first, classic rheumatoid spondylitis later develops. (4) The pathologic reactions in the vertebral apophyseal joints of patients who have rheumatoid spondylitis are said to resemble those of classic rheumatoid arthritis without spondylitis.

The pathologic processes that are present in rheumatoid spondylitis have been



studied histologically insofar as affected apophyseal joints of the spinal column and involved peripheral joints are concerned. As yet pathologic studies of the sacro-iliac joints in the active stage of the disease have not been reported; the only ones reported have been made in the late stage after ankylosis has occurred. Specimens taken from affected apophyseal spinal and peripheral joints in cases of rheumatoid spondylitis have shown the changes identical with those seen in rheumatoid arthritis without spondylitis.<sup>2,14</sup> According to Dunham and Kautz,<sup>5</sup> Guntz found that in the apophyseal joints of the spinal column in the early stages of the disease there was inflammation of joint surfaces with exudation, invasion of the cartilage with round cells and production of connective tissue. After further progress of the disease only islands of cartilage remained and finally ankylosis occurred. Early in the disease all of the apophyseal joints of the spinal column were not involved but the process was never limited to 1 or 2 joints. He found the same pathologic process in the costovertebral joints. According to Boland and Shebesta,<sup>2</sup> J. E. Flynn stated that pathologic specimens taken from apophyseal joints during the active phase of rheumatoid spondylitis revealed microscopic findings similar to those seen in peripheral rheumatoid arthritis.

Rheumatoid spondylitis may occur in persons of any age according to Polley and Slocumb.<sup>15</sup> Their youngest patient was 4 years of age and the oldest 63 years of age. They found the average age of onset to be 26.7 years. In 80% of their cases the symptoms first appeared when the patients were between 15 and 35 years of age. Men were affected 9 times more frequently than women. Thus it is obvious that rheumatoid spondylitis is a disease that affects young men predominantly. The importance of this is shown by the observation of Boland and Present<sup>1</sup> that 18% of the patients with chronic back complaints who were admitted to an army general hospital were found to have

rheumatoid spondylitis. They also noted that, although in civilian life the ratio of rheumatoid spondylitis to rheumatoid arthritis is 1/6, according to the best figures, in the Army the relative incidence was 1/3 or 1/2. This they attributed to the fact that rheumatoid spondylitis has a predilection for men of military age and that strenuous physical exertion brought to light cases of mild or early rheumatoid spondylitis, including many cases in which the disease was present before the patient was inducted into the Army but was not recognized.

Far-advanced rheumatoid spondylitis can be recognized with ease but when the disease is this extensive it does little good to make the diagnosis, since little can be done in the way of treatment. The diagnosis must be made early in the course of the disease if benefit is to be expected from treatment. Many of the early symptoms are vague and indefinite, but a few may be objective. The unwary physician may easily overlook the true nature of the condition. Boland and Present<sup>1</sup> noted that in many cases the condition was mislabeled as lumbago, fibrositis, muscular rheumatism, chronic low back strain, renal disease or idiopathic sciatica. Krebs<sup>11</sup> found that because definite objective findings are absent early in the disease, patients were often considered malingerers or neurotic. Polley<sup>14</sup> found that in 41 of the 1035 cases he studied operation had been performed at one time or another because the symptoms were not recognized as those of early rheumatoid spondylitis but were attributed to some condition requiring an operation. The surgical procedures that he listed are most interesting and reveal the deceiving nature of rheumatoid spondylitis. They were: operations for protruded intervertebral disks; spinal fusions; laminectomy; biopsy of hip for suspected tuberculosis; synovectomy of knee and ankle; surgical drainage of the knees; arthrodesis of foot and ankle; removal of piece of bone from foot; abdominal fasciectomy to correct posture; fasciotomy of

hips; removal of calcaneal bursæ bilaterally; removal of bilateral calcaneal spurs; appendectomy; hysterectomy and cholecystectomy; thyroidectomy; repair of right inguinal hernia; appendectomy, salpingectomy and oöphorectomy; hysterectomy and oöphorectomy. Almost none of the patients received any benefit as result of the operation. Polley<sup>14</sup> also found that in 10% of his cases some anomaly of the spinal column was present such as sacralization of the last lumbar vertebra, spina bifida occulta, spondylolisthesis, cervical rib or anomalies of the sacrum and coccyx. In some cases these anomalies probably were considered the cause of the symptoms that were present.

It is obvious, therefore, that the early symptoms of rheumatoid spondylitis are often misleading and that a review of these symptoms and the methods of early diagnosis are warranted. Especially is it pertinent that this disease be discussed more frequently at present, as the operation for the removal of the protruded intervertebral disk has become a frequent remedy for the relief of low backache and sciatica and rheumatoid spondylitis may mimic the syndrome of protruded intervertebral disk.

**THE DIAGNOSIS OF EARLY RHEUMATOID SPONDYLITIS.** The diagnosis of early rheumatoid spondylitis is not too difficult, as a rule, if that condition is thought of and considered as a cause of the patient's symptoms. But all too frequently rheumatoid spondylitis is not even considered. For this reason the early symptoms of this condition must become more widely known by physicians. Boland and Shebesta<sup>2</sup> have ably described these symptoms:

"Because the disease almost invariably begins in the sacro-iliac joints, the symptoms and findings referable to the lower back at onset may be considered as expressions of sacro-iliac involvement. In approximately 75% of cases the early symptoms consist of aching and stiffness of the lower back, which qualitatively exhibit the characteristics of

'fibrositis,' that is, are most pronounced on arising in the morning, are accentuated by physical inactivity and ameliorated by mild exercise, are subject to fluctuations with weather changes, and are relieved temporarily by local heat and salicylates. At first, these symptoms may be intermittent, but after several months or a few years they tend to become persistent. Transient sharp pains or 'catches' in the lower back or less well-defined complaints, as constant dull discomfort, a soreness, or a tired feeling (accompanied or unaccompanied by symptoms of 'fibrositis') may also indicate sacro-iliac involvement. In 10 to 15% of cases sciatica, often intermittent and alternating from side to side, accompanies the phase of sacroiliitis.

"The back may be entirely normal on examination. In about 50% of patients with active sacroiliitis, tenderness on percussion may be elicited over 1 or both sacro-iliac joints. Orthopedic tests causing motion in the sacro-iliac joints may induce pain. Mild muscle spasm in the lumbar region without true restriction of motion is common.

"When the disease is active in the lumbar, thoracic and cervical regions, the dominant symptoms consist of pain, aching, stiffness, and restriction of motion in the involved regions. Sciatica is common with lumbar involvement, girdle pains are frequent when the thoracic spine is affected, but cervical radicular pain is rare. Lumbar, thoracic, or cervical involvement may be identified by the presence of the following general signs in the respective regions of the back: limitation of motion; persistent paravertebral muscle spasm; persistent tenderness to percussion over and just lateral to the spinous processes; pain on forced motion of the spine; paravertebral muscle atrophy. Involvement of the lumbar spine is further characterized by straightening of the normal lordotic curve and by muscle atrophy in the lower portion of the lumbar segment, giving this area an 'ironed-out' appearance. Thoracic involvement may be further identified by chest pain on deep inspiration, restricted respiratory excursion, flattened anterior chest, and thoracic kyphosis. A characteristic protruded position of the neck may develop when the cervical spine is involved."

Polley<sup>14</sup> emphasized the tendency for exacerbations and remissions as well as

the shifting character of the early symptoms of rheumatoid spondylitis. He further noted that sciatica was the first symptom in 10% of cases and that in 10% more it developed later in the course of the disease. This is of great importance since physicians often make the diagnosis of protruded intervertebral disk when sciatic pain is present. Polley also found that in 23.4% of his cases the first symptoms indicated disease of the peripheral joints and these tended to disappear without any apparent residual damage to the joint.

The sedimentation rate is a helpful laboratory test. It is in no way specific, but if the rate is abnormally high it does indicate that the patient's symptoms are not psychogenic and that an active pathologic process is present. Boland and Shebesta<sup>2</sup> have made it clear, however, that although the sedimentation rate fairly consistently gauges the activity of rheumatoid spondylitis and roughly parallels the severity of the disease, in 15 to 20% of cases of mild but clinically active rheumatoid spondylitis it is normal. Polley and Slocumb<sup>15</sup> also found the sedimentation rate normal in nearly a fifth of their cases. Therefore it must be kept in mind that although an abnormally high sedimentation rate may be evidence in favor of rheumatoid spondylitis, a normal sedimentation rate does not exclude that disease. Patients who have rheumatoid spondylitis often have moderately severe, hypochromic anemia, but this is not of much importance in diagnosis.

*Roentgenologic Diagnosis.* Roentgenologic manifestations are of prime importance in the diagnosis of early rheumatoid spondylitis. The roentgenologist's help in the diagnosis of this disease may be in 1 of 2 ways: He may suggest the presence of rheumatoid spondylitis in cases in which that condition is not suspected clinically. This occurs not infrequently and is of inestimable value to the clinician. Secondly, he can confirm the clinical impression that rheumatoid spondylitis is present, a confirmation by roentgenologists,

many clinicians are reluctant to make a definite diagnosis of rheumatoid spondylitis but prefer to watch the patient closely until roentgenologic evidence of the condition is present. As mentioned previously, however, those who have had great clinical experience with this disease at times can make an accurate diagnosis before changes are apparent in the roentgenograms.

The roentgenologic diagnosis of early rheumatoid spondylitis depends primarily on changes that are seen in the sacro-iliac joints. The importance of the destructive changes seen in the sacro-iliac joints was first emphasized by Krebs,<sup>11</sup> Krebs and Vontz,<sup>12</sup> and Scott,<sup>16</sup> and later verified by Forestier.<sup>6</sup> Other investigators<sup>1,2,5,9,14,15</sup> have concurred recently in the belief that the changes in the sacro-iliac joints are the most important roentgenologic manifestations of the disease. Hench, Slocumb and Polley<sup>9</sup> stated: "The most useful single laboratory aid in the diagnosis of rheumatoid spondylitis consists in roentgenographic examination of sacro-iliac joints. Although there is an appreciable lag between the development of physical findings and roentgenographic alterations, this lag is generally more than counterbalanced by the patient's tardiness in consulting a physician. Hence, even in fairly early cases roentgenograms generally already reveal sacro-iliac alterations."

In 1934, Scott<sup>16</sup> found that in 98% of 1035 cases of rheumatoid spondylitis the sacro-iliac joints as shown roentgenologically were involved. Similarly Boland and Present<sup>1</sup> found that sacro-iliac changes had occurred in all of the 100 cases that they studied. They even hesitated to make a clinical diagnosis of rheumatoid spondylitis if the sacro-iliac joints appeared normal. Forestier<sup>6</sup> found that there was no demonstrable sacro-iliac involvement in only 2 of 135 cases, whereas in 12 cases changes in the sacro-iliac joints were not associated with roentgenologic

evidence of vertebral involvement. Cases were reported by Buckley<sup>4</sup> and Gordon<sup>7</sup> in which there was no roentgenologic evidence of sacro-iliac disease. Key and associates<sup>10</sup> studied the bones of 2 patients with rheumatoid spondylitis who died and who had vertebral involvement but who had no changes in the sacro-iliac joints. Oppenheimer<sup>12</sup> and Borak,<sup>3</sup> although recognizing that changes in the sacro-iliac joints were frequent, stated that the diagnosis must be based on roentgenologic evidence of alteration in the vertebral apophyseal joints.

Most investigators have found that the roentgenologic demonstration of disease of the apophyseal joints of the spinal column is difficult and not reliable as a basis for the diagnosis of early rheumatoid spondylitis. The apophyseal joints must be studied by means of roentgenographic views taken at special angles and since the plane of the apophyseal joints varies greatly, it is often necessary to take several views at different angles. Oppenheimer,<sup>12</sup> who has contributed much to our knowledge of changes in the apophyseal joints, mentioned the difficulty of demonstrating these changes roentgenologically. Boland and Shebesta<sup>2</sup> found changes in the apophyseal joints in only 9 of their 50 cases, and Boland and Present<sup>1</sup> never found the apophyseal joints involved unless the sacro-iliac joints were affected also. If the roentgenologist is to find evidence of rheumatoid spondylitis in patients in whom this disease is not suspected clinically, he must do this by means of routine roentgenographic views and, therefore, he most certainly must depend on the changes in the sacro-iliac joints rather than those in the apophyseal joints.

The earliest changes of rheumatoid spondylitis that occur in the sacro-iliac joints are not always easy to recognize in the roentgenogram. These do not consist of marginal sclerosis, as some investigators have stated, but instead, as Forestier noted, the contour of the subchondral bone of the sacro-iliac joint becomes indistinct and hazy; the joint loses its clear-

cut margins and becomes indistinct. This marginal decalcification causes the joint to appear widened. Somewhat later sclerosis begins to appear at the margins of the joints. This osteosclerosis may be spotty and mottled and at this stage the margins of the joint are even more indistinct. The process gradually progresses until there is loss of the joint space and fibers of bone are seen growing across this space. These osseous fibers are the first evidence that ankylosis is developing and this process progresses until ultimately there is smooth bony ankylosis of the joints. If the diagnosis of rheumatoid spondylitis is to be made early in the course of the disease, the roentgenologist must search carefully for those early manifestations of the disease which consist of decalcification at the margins of the joint with resultant indistinct outlines of the joint. A moderate degree of marginal sclerosis occurs fairly early many times but dense sclerosis of the bone and ankylosis are late manifestations of the disease. At times only 1 sacro-iliac joint will show evidence of disease; Polley<sup>14</sup> noted this unilaterality in 6 of his 1035 cases.

Roentgenologic evidence of vertebral involvement almost always appears much later than that of sacro-iliac involvement. In routine lateral roentgenologic views the first apparent change in the vertebrae indicative of rheumatoid spondylitis is a peculiar "squaring-off" of the vertebral bodies. This change usually is evident in the thoracolumbar region first and it is due to fine calcification of the anterior longitudinal ligament which causes a filling in of normally concave anterior vertebral surfaces and "squares off" the anterior vertebral angles. Later in the course of the disease calcification of the vertebral ligaments is more obvious and appears in the roentgenogram as fine lines of calcification which cross from the margin of one vertebral body to the next. At first this process can be seen only in 1 or 2 interspaces, usually in the lumbar region. Later the ligamentous calcification becomes dense and more extensive

and gradually involves all the vertebral ligaments until the entire spinal column is involved. The end-result is the so-called bamboo spine.

Although involvement of the apophyseal joints of the spinal column occurs earlier than vertebral calcification, changes in them are more difficult to see when routine views are used and as stated before, even when views taken at special angles are used the alteration in these joints still cannot be seen many times. The earliest change in these joints is decalcification of the articular surfaces which then appear indistinct in the roentgenogram. Marginal osteosclerosis can be seen at times and this process may progress to ankylosis, as in the sacro-iliac joints. Osteoporosis of the vertebræ is almost always seen after the spine has begun to be immobilized, but this is not an early manifestation of the disease. The intervertebral disks are not involved early but at times very late in the course of the disease there may be involvement of an occasional interspace; the vertebral surfaces become irregular and indistinct. Also as a late manifestation the costo-vertebral articulations may be involved and ankylosis is the end-result. The symphysis pubis may be affected and not infrequently the ischial tuberosity will show irregularity and bony proliferation. This last change is probably the result of involvement of the adjacent ischial bursa by the inflammatory process.

Occasionally definite roentgenologic evidence indicates that the disease has affected 1 or both hips. The appearance is identical with that caused by rheumatoid arthritis with narrowing of the joint space and decalcification and indistinctness of the articular surface. In a few cases other peripheral joints will show similar roentgenologic evidence of involvement.

*Differential Diagnosis.* Changes in the spinal column due to hypertrophic arthritis, so-called osteo-arthritis, can be distinguished from those of rheumatoid spondylitis with ease as a rule. As

Forestier<sup>6</sup> has noted, osteophytes have a thick base, are covered with a cortex which comes from that of the vertebral body and have a structure of cancellous bone like the vertebral body itself. The syndesmo-phytes of rheumatoid spondylitis are clear-cut, linear calcifications without a cortex and look like a thin or thick comma added to the contour of the vertebral body. Dunham and Kautz<sup>5</sup> listed the following characteristics of osteo-arthritis: (1) it occurs after the 4th decade of life in 80% of cases; (2) the sedimentation rate is not elevated; (3) fever and leukocytosis are uncommon; (4) degeneration of the intervertebral disks is present; (5) osteophytes, but no syndesmophytes are present; (6) wedging of the vertebral bodies occurs; (7) there may be true bony bridging between vertebral bodies; (8) occasionally there is coarse calcification on the anterior surface of the vertebral column in the thoracic region. Destructive changes never are seen in the sacro-iliac joints in this condition. Ankylosis of the sacro-iliac joints are found not infrequently as a senile change but not as the result of infection. Hypertrophic changes are seldom seen in the sacro-iliac joints except as the result of abnormal weight bearing as in marked scoliosis and then only 1 sacro-iliac joint is affected as a rule and the rather sharp marginal osteitis does not resemble that produced by rheumatoid spondylitis.

A condition, known as "osteitis condensans ilii," was described, according to Hare and Haggart,<sup>8</sup> by Sicard, Gally and Haguenu in 1926. Hare and Haggart<sup>9</sup> recently reported cases and reviewed the subject. It has only 1 resemblance to rheumatoid spondylitis and that is that osteosclerotic changes appear in the sacro-iliac joints. This condition is found almost exclusively in women. Roentgenologically dense sclerotic bone may obliterate the trabeculae in the articular portion of the ilium and the portion of the ilium adjacent to the sacro-iliac articulations. The demarcation between normal and abnormal bone is distinct. The involve-

ment is usually bilateral but it has been reported in only 1 joint. The etiology is unknown. The condition is rare, but when it does occur, it is frequently during or after pregnancy. It is characterized by recurrent attacks of chronic low backache. The sedimentation rate is never elevated. Its resemblance to rheumatoid spondylitis is superficial.

Unilateral destructive changes in the sacro-iliac joints due to tuberculosis or osteomyelitis are seen at times. There is not much resemblance to rheumatoid spondylitis when this occurs.

The roentgenologic manifestations of rheumatoid spondylitis, therefore, appear distinctive and do not seem to resemble closely those of any other conditions which involves the spinal column and sacro-iliac joints. The most important factors in the roentgenologic diagnosis of early rheumatoid spondylitis are close scrutiny of the sacro-iliac joints and the ability to recognize the early manifestations of the disease as it affects these joints.

Boland and Present<sup>1</sup> have listed the following conditions under which rheumatoid spondylitis should be suspected and it would be well if all physicians were well acquainted with these.

"1. Suspect rheumatoid spondylitis when a young man complains of chronic recurrent or persistent low back aching and stiffness, with or without catching pains, especially if the sedimentation rate is elevated.

"2. Suspect rheumatoid spondylitis in the young man who complains of such vague symptoms as a 'tired feeling' in the lower part of the back on standing and walking, persistent low back soreness, silent restriction of back motion, or indefinite sharp pains in the buttocks, hips or lower part of the back, especially if accompanied by an elevated sedimentation rate or general constitutional symptoms.

"3. Suspect rheumatoid spondylitis in all cases of sciatica in young men, particularly if recurrent or alternating from side to side or associated with aching and stiffness of the lower back.

"4. Suspect rheumatoid spondylitis in

patients with thoracic girdle pains, especially if accompanied by symptoms in the lower part of the back.

"5. Suspect rheumatoid spondylitis when persistent back symptoms develop in a patient with peripheral rheumatoid arthritis.

"6. In the absence of roentgenographic evidence of sacro-iliac involvement an unequivocal diagnosis of rheumatoid spondylitis should not be made unless characteristic changes are present in the apophyseal joints.

"7. Remember that characteristic Roentgen ray changes in the sacro-iliac or apophyseal joints may not develop for months after the onset of symptoms. Do not eliminate the possibility of rheumatoid spondylitis on negative Roentgen rays alone unless persistent symptoms have existed for at least 3 years.

"8. Definite bilateral destructive and/or sclerotic changes in the sacro-iliac joints, noted roentgenographically, almost invariably indicate rheumatoid spondylitis.

"9. Be cautious in making a diagnosis of rheumatoid spondylitis with unilateral sacro-iliac involvement unless other characteristics of the disease are present or unless peripheral rheumatoid arthritis coexists. Persistent unilateral sacroiliitis may be due to tuberculosis.

"10. Calcification of the paravertebral ligaments may result from several causes and in itself is not sufficient evidence for the diagnosis of rheumatoid spondylitis; changes in the apophyseal and/or sacro-iliac joints must also be present.

"11. Remember that the sedimentation rate may be normal in 15 to 20% of cases with active disease and that constitutional symptoms are usually milder than in rheumatoid arthritis involving peripheral joints.

**Summary.** The symptoms of early rheumatoid spondylitis are often misleading. As a result the symptoms often are either dismissed as unimportant or are attributed to some other disease.

Roentgenologic manifestations of early rheumatoid spondylitis are often sufficiently definite so that their presence alone provides sufficient evidence for a definite diagnosis of that condition or for confirmation of the clinical impression that rheumatoid spondylitis is present.

Destructive changes in the sacro-iliac joints are definite evidence of rheumatoid spondylitis, especially when there is bilateral involvement.

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# BOOK REVIEWS AND NOTICES

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DISEASES OF THE ADRENALS. By LOUIS J. SOFFER, M.D. Pp. 304; 42 ills.; 2 color plates. Phila.: Lea & Febiger, 1946. Price, \$5.50.

THIS is a systematic and interestingly written presentation of diseases of the adrenal glands. Physiologic and chemical studies are reviewed in such a way as to give an historical background and to bring up to date the experimental and clinical research which has permitted a scientific approach and understanding of the structural and functional changes seen in man. Certain practical features include the actual techniques of chemical methods used in clinical diagnosis. Case histories and many illustrations have been selected with a view to their usefulness to clinicians. This book can be highly recommended to those interested in theoretical and practical aspects of endocrinology. I. Z.

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HOSPITAL CARE IN THE UNITED STATES. A Study of the Function of the General Hospital, Its Rôle in the Care of All Types of Illness, and the Conduct of Activities Related to Patient Service, With Recommendations for Its Extension and Integration for More Adequate Care of the American Public. By the COMMISSION ON HOSPITAL CARE. Pp. 631; 94 tables, 58 charts. New York: The Commonwealth Fund, 1947. Price, \$4.50.

THE Commission of 22 members responsible for this report, under the Chairmanship of Thomas S. Gates of the University of Pennsylvania, was drawn from many fields: medicine, public health, hospital administration, nursing, dentistry, social agencies, education, agriculture, industry and labor. The director of the study was A. C. Bachmeyer, M.D.

According to the report, our present rather haphazard development of hospital service will not meet our needs for the future; the base of hospital support must be broadened, and hospital service must be strengthened and made available for all. The Commission completed a pilot study in Michigan.

Its procedure, based upon this pilot study, has been adopted in 40 states where hospital surveys are under way.

The report furnishes a plan for analyzing the hospital facilities and needs of any area and a program for integrating and extending hospital service to improve the organization and distribution of hospital care. Quantitative data are abundant and are reflected in the large number of tables and line charts. The statistical analysis of these data is fruitful and stimulating.

The conclusions and recommendations are conservatively formulated. They encourage careful study and analysis of local conditions in each community rather than easy acceptance of superficially conceived general formulas, a commendable feature of this report. The report will interest a wide group of civic minded citizens as well as the members of the professions most directly concerned. J. A.

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SIR W. ARBUTHNOT LANE, Bart., C.B., M.S., F.R.C.P., HIS LIFE AND WORK. By W. E. TANNER, M.S., F.R.C.S. Pp. 192; 1 ill. Baltimore: Williams & Wilkins, 1946. Price, \$4.50.

THE author of this handsomely written and fair-minded book probably over enthusiastically places Lane "next to Lister on the scroll of the British pioneers of surgery." Like all pioneers and like all great men who "always saw the good in people," Lane was sometimes deceived both by theories and by people, and so was sometimes seriously mistaken. Time has most conspicuously proved him wrong in his views upon intestinal stasis; but, as Mr. Tanner convincingly writes, now in 1946: "The real disorder may have been in the patient's brain or vago-sympathetic system. By his brave and great experiment of colectomy, Lane has proved this. Let us be thankful that no lesser hand has shown this fundamental truth!" This tribute from one surgeon to another is more than loyal and understanding defense; it is sound and leads with admirable logic to the quotation from Carlyle that heads the Epilogue to this



excellent book: "The errors of a wise man are literally more instructive than the truth of a fool."

E. T.

**CUSHNY'S PHARMACOLOGY AND THERAPEUTICS.** By ARTHUR GROLLMAN, Southwestern Medical College, and DONALD SLAUGHTER, Univ. of South Dakota. 13th ed. Pp. 868; 74 ills., Phila.; Lea & Febiger, 1947. Price, \$8.50.

In this edition of a classic text the two new editors have added large sections on recent drugs, making it the first pharmacology textbook to treat streptomycin and other antibiotics, folic acid, antihistamine compounds and the newer sulfonamides. These and other completely new sections are well written, clear, concise and up-to-date. They are responsible in large part for the value of the book as a text for student and physician. It is not only the newer drugs, however, which get such thorough treatment. The 31 page section on digitalis drugs has been revised to include the newer active principles in increasing usage today and a complete consideration of the clinical aspects of digitalis therapy illustrated with numerous electrocardiograms. Turning to other sections, however, one is somewhat disappointed to find the revision spotty and sometimes inadequate. Advances in our understanding of the mechanism of action and therapeutic use of some of the older drugs do not always find their way into the text. More stress on the clinical actions of drugs might be useful to the physician interested in rational therapy and better annotated bibliographies would help the student interested in outside reading. On the other hand the index has been made larger and more complete and the concise listing of official preparations at the end of each section add much to the convenience of the book.

S. K.

**GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY, WITH CLINICAL AND ENDOCRINE RELATIONS.** By EMIL NOVAK, A.B., M.D., D.Sc. (Hon. Dublin), F.A.C.S., Assoc. in Gyn., Johns Hopkins Medical School. Pp. 570; 542 ills.; 15 in color. 2nd ed., Philadelphia and London: W. B. Saunders Co., 1947. Price, \$7.50

This book was written both for practical value to the clinician and the pathologist.

The author is admirably qualified for his task since he is an accomplished clinician who has attained preëminence in the fields of both gynecological endocrinology and gynecological pathology.

The new edition contains 75 more pages and 115 more illustrations than its predecessor. The recent developments in obstetrical and gynecological pathology are included with valuable appraisals of the vaginal smear in the diagnosis of uterine cancer and of the newer concepts concerning erythro-blastosis foetalis.

Two outstanding portions of the book are devoted to carcinoma of the cervix and to ovarian tumors. The microscopic diagnosis, or exclusion of early cervical malignancy, is presented lucidly and the accompanying illustrations are particularly clear. Perhaps it might appear that too much space is devoted to the special ovarian tumors—half of the section—and too little space to the commoner ones, but this apparent over-emphasis is justified by recent great interest in the rare ovarian tumors and by the authoritative knowledge of this subject possessed by the writer.

This volume is recommended to both the gynecological pathologist and the clinician because of its great informative value and its easy readability.

F. P.

**HANDBOOK OF PHYSIOLOGY AND BIOCHEMISTRY.** By R. J. S. McDOWALL, M.D., D.Sc., Professor of Physiology, Univ. of London, King's College. 39th ed. Pp. 898; 305 figs. Phila.: Blakiston, 1946. Price, \$7.00.

THERE are not many texts that have stood the test of time covering four years short of a century. Professor McDowall of King's College has been the editor since 1930 when he succeeded Professor Halliburton, who was editor from 1896.

This edition differs from the 38th in that the chapters on histology have been drastically reduced to sections on the relation of function to structure.

This book is still unique in that it brings together information not found in single physiological or biochemical texts of a comparable class.

An interesting commentary on what should be omitted from a medical curriculum is made by the author, namely: "it will do

no harm if the student catches a fleeting glance of things he need not know, for soon he will realize his knowledge of Medicine generally must of necessity be most patchy and superficial." J. S.

A HISTORY OF THE AMERICAN MEDICAL ASSOCIATION, 1847-1947. By MORRIS FISHBEIN, M.D. With the Biographies of the Presidents of the Ass'n. By WALTER L. BIERRING, M.D., and with Histories of the Publications, Councils, Bureaus, and Other Official Bodies. Pp. 1226; 200 ills. Phila., and London: W. B. Saunders, 1947. Price, \$10.00.

THIS work, in preparation for several years under the charge of a special committee of the Association, appropriately made its appearance just in time for the Centennial celebration of the Association. Big and weighty as the book is, it is none too large for the accomplishment of its aim—as a record, in the words of the Publication Committee, “of its founder, its founding, its ideals, its motivations and the extent to which these have been accomplished over a period of 100 years.” This aim of giving a factual picture as detailed as possible of the largest and probably the most influential medical society that the world has ever seen has been well carried out, so that the book will undoubtedly be permanently the standard source of reference for those seeking information on this subject. It will be a necessary possession of every medical reference library, as well as of most city, county and state medical societies. It is obvious however, that it cannot also serve the individual to any great extent as pleasant continuous reading matter. As this type of reader and even the general public are said to have been in mind, one wonders why objections to a format of two smaller volumes prevailed.

The text contains much, especially that to do with the activities of the last quarter century, that has not previously appeared in print. Following a brief biography of Nathan Smith Davis, who also wrote a history of the Association that he founded, comes Dr. Fishbein's History, occupying almost half the volume. Though the limitations of the factual record mentioned above are apparent here as elsewhere, the well known adroitness and literary ability of the author has kept them at a minimum. Parenthet-

ically, one regrets that “Dr. Pepys” did not choose to lighten his narrative, even in this serious production, with more of his free flowing humor. He has woven into his account interesting considerations of such topics as the early troubles of the Association and its reorganizations, Simmons as editor, quackery, the Journal, animal experimentation, improvement of medical care, the trend toward socialization of medicine, ending with the recent trial by the U. S. Government. When the reader turns to the index to combine such material into connected reading units, its inadequacy—only 16 pages for both persons and subjects—is immediately felt. To the Reviewer this constitutes the most serious defect in the production. Especially for a work written primarily as a factual record, how can the numerous subjects, many turning up many times through the book, be adequately indicated in 8 pages? “Nostrums,” for instance, appear in the subject index only as part of the title of a book, though actually receiving lengthy treatment in the libel suit section and several other places. Dr. Bierring's biographical sketches of the 100 presidents, each accompanied by a portrait, occupy 260 pages. Those of which the Reviewer has personal knowledge all appear adequate; together they make a useful reference source. It is of interest, and an indication of the qualifications sought in candidates for this office as well as of the position of organized medicine in this country, that fewer than a third of those elected in the first half century were known to the Reviewer, whereas in the last half century more than half, at the moment at least, have claim to eminence. The remaining space in the book is occupied by brief accounts of the Councils and Bureaus of the Association, and its publications, and various lists gathered into Appendices.

The preparation of the volume was delegated to W. B. Saunders Co., who have brought it out in a form worthy of both Association and publishing house. It is a creditable record of an organization that inevitably has had to struggle with many internal shortcomings; but this perhaps should not even be mentioned when they have been so far outweighed by the many contributions to the advancement and elevation of the practice of medicine of this great Association.

E. K.

## BOOK REVIEWS AND NOTICES

**RH: ITS RELATION TO CONGENITAL HEMOLYTIC DISEASE AND TO INTRAGROUP TRANSFUSION REACTIONS.** By EDITH L. POTTER, M.D., Ph.D., Ass't. Prof. of Pathology, Dept. of Obstetrics and Gynecology, Univ. of Chicago and Chicago Lying-in Hospital. Pp. 344; 65 ills., 16 tables. Chicago: Year Book Publishers, 1947. Price, \$5.50.

This excellent monograph will prove valuable to the clinical laboratory, the blood bank, the obstetrician and pediatrician, and to the general clinician, in a field of great importance, the development of which has occurred almost entirely in the last few years.

In a foreword, L. K. Diamond points out the exceptional qualifications of the author for the task she has undertaken and warmly endorses this work. The history of our knowledge of the various Rh antigen and antibodies and the resulting types as they occur in various races is set forth, and the different systems of terminology are compared and related. The description of the Hr factors and of the blocking antibodies is excellent and especially timely. The etiology, symptomatology, diagnosis and pathology of "Hemolytic Disease," the name preferred by the author for what has often been called erythroblastosis foetalis, is presented in great detail in a chapter of 160 pages, with excellent illustrations of blood changes and of gross and histological pathology. The significance of the S Rh blood types in cases of disputed parentage is tabulated and briefly discussed. Pertinent laboratory techniques are assembled in a final chapter of 36 pages, with photographs and drawings of apparatus and of reactions. The bibliography contains 794 references, extending through at least November, 1946.

While the important contributions of various workers in this field are utilized with due credit given, this work is a unified presentation of the subject based on the experience of the author and not a mere collection of observations from the literature. Clinician, laboratory worker and student will find the currently available information with respect to this difficult and very important field clearly and readably presented.

J. A.

**WAR STRESS AND NEUROTIC ILLNESS.** By ABRAHAM KARDINER, M. D., Assistant Clinical Professor of Psychiatry, Columbia Univ., with the collaboration of HERBERT SPIEGEL, M.D., formerly Major M.C., A.U.S., Instructor School of Military Neuropsychiatry, Mason General Hospital. Pp. 428; 3 tables. 2nd ed. New York: Paul B. Hoeber, 1947. Price, \$4.50.

This study, including 40 case reports, concerns the nervous syndrome consequent upon the stress of war, and variously known as traumatic neurosis, shell shock, battle fatigue, combat exhaustion, and so forth. Though the reason is not definitely known, there were relatively few "extreme hysterical abasias, paralyzes, and the epileptiform types of traumatic neurosis in World War II."

Following the Introduction, the chapters are: The Soldier and His Job; Battlefield Psychiatry; The Acute Phase; Treatment of the Acute Phase; The Chronic Phase—Symptomatology; Analysis of the Symptomatology; Development of the Effective Ego; Psychodynamics; Treatment of the Chronic Phase; Course, Prognosis, Differential Diagnosis; Forensic Issues.

Symptoms of the acute phase are those of a cross-section, with the following prodromal manifestations: loss of appetite, carelessness, jumpiness, freezing to the ground, marked irritability, incapacity for relaxation and disturbed sleep; fear or terror sometimes follows. Then the subject may show confusion or depression. Symptoms of the chronic phase vary with the trends shown by the personality. Among the important findings are hypochondriasis, schizophrenia, transference neurosis, defensive ceremonials and ties, autonomic disturbances; psychosomatic disorders, and the epileptic symptom complex. The section on the chronic phase includes the important additions found in the current edition, namely, the uses of barbiturates and hypnosis to render the subject more accessible; the former has the advantage of being an anesthetic, but the disadvantage of blunting the sensorium; the latter, renders the emotional tone more vivid and the reconstruction more effective. This collaborative study is a valuable contribution to our better understanding of the war stress neurosis.

N. Y.

**THE TREATMENT OF DIABETES MELLITUS.**

By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., Clinical Professor of Medicine Emeritus, Harvard Medical School, Medical Director, Baker Clinic, New England Deaconess Hospital. 8th ed. Pp. 861; 6 ills.; 117 tables. Phila.: Lea & Febiger, 1946. Price, \$10.00.

THIS edition of the most complete text on diabetes follows the general outline of the preceding edition. A new chapter on alloxan diabetes affords the best review of this subject to date. Extensive revision of the chapters on the genito-urinary system and on pregnancy in diabetes is noted. Throughout the book the statistics, tables and references have been brought up to 1946, so that the large experience of this Clinic and a wealth of literature is made available in one volume. The 300 or more pages on complications and concurrent conditions are the only such comprehensive source of information on the interrelation of diabetes and other diseases.

One gains the impression that valuable nuggets are often concealed in this mine of information. Improved organization of the book as a whole, more detailed indexing and bibliographies with full titles after each chapter might be helpful. These thoughts for future editions occur to a reviewer who has profound admiration for what is accomplished by this book.

F. L.

**RADIOLOGY FOR MEDICAL STUDENTS.**

By F. S. HODGES, M.D., I. LAMPE, M.D., and J. F. HOLT, M.D., Univ. of Michigan. Pp. 424; 103 ills. Chicago: The Year Book Publishers, 1947. Price, \$6.75.

THE authors of this book have provided for the medical student a comprehensive, yet brief, insight into Radiology. The book is beautifully prepared on excellent paper with good print and excellent illustration and explanatory drawings. There are 15 chapters, 7 of which are devoted to diagnostic Radiology, and the remainder to therapeutic Radiology.

The modern physician employs Radiology in almost every specialty. It is, therefore, necessary that the medical student become conversant with the indications and limitations of x-ray diagnosis. Likewise, it is important for the medical student to be familiar with the various components of the

atom and their effect upon tissue. The increasing use of radioactive isotopes in diagnosis and therapy has extended into fields other than Radiology. In fact, they are being used in almost every specialty in medicine. The authors of this book have kept this in mind in preparing their textbook.

It is difficult to avoid being too enthusiastic about this text. It is the type of text that will be exceedingly useful to every teacher in Radiology.

E. P.

**ADVANCES IN CARBOHYDRATE CHEMISTRY.**

Vol. II. Edited by W. W. PIGMAN, B.S., A.M., Ph.D., Institute of Paper Chemistry, Appleton, Wis.; M. L. WOLFROM, A.B., M.S., Ph.D., Ohio State Univ., Columbus, Ohio, and STANLEY PEAT, The University, Birmingham, England. Pp. 323. New York: Academic Press, 1946. Price, \$6.60.

WITH this 2nd volume "Advances" becomes international in scope. Four chapters are contributed by English chemists and 1 each from France and Canada, while the remaining 4 come from American authors.

The following subjects are reviewed: Melezitose and Turanose, by C. S. Hudson, 34 pages; The Chemistry of Anhydro Sugars, by S. Peat, 39 pages; Analogs of Ascorbic Acid, by F. Smith, 27 pages; Synthesis of Hexitols and Pentitols from Unsaturated Polyhydric Alcohols, by R. Lespieau, 11 pages; The Interrelation of Carbohydrate and Fat Metabolism, by H. J. Deuel, Jr. and M. G. Morehouse, 43 pages; The Chemistry of Nucleopolysaccharides and Mucoproteins, by M. Stacey, 39 pages; Bacterial Polysaccharides, by T. H. Evans and H. Hibbert, 29 pages; The Chemistry of Pectic Materials, by E. L. Hirst and J. K. N. Jones, 16 pages; The Polyfructosans and Difructose Anhydrides, by E. J. McDonald, 24 pages; Cellulose Ethers of Industrial Significance, by J. F. Haskins, 14 pages.

All authors are recognized specialists in their topics, and they present a concise summary of present knowledge. The articles by Deuel and Morehouse, Stacey, and Evans and Hibbert in particular are of biochemical interest. Mucopolysaccharides and bacterial polysaccharides have been investigated actively in recent years, yet have not been the subjects of reviews elsewhere. The present reviews are, therefore, appropriate and timely.

H. V.

**PENICILLIN IN NEUROLOGY.** By A. EARL WALKER, M.D., and HERBERT C. JOHNSON, M.D. Pp. 204; 95 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, \$5.00.

This is an excellent book containing all the latest information, as of 1946, on the use of penicillin in counteracting infection, both acute and chronic, in the central nervous system. Unfortunately, as is the case in all such publications, as new studies and improvements in the therapeutic use of any drug are made, the information rapidly becomes out-of-date.

The treatment of acute or chronic infections of the central nervous system with penicillin faces at once the problem of the passage of the penicillin through the hemato-encephalic barrier, so that the drug reaches the cerebrospinal fluid and the substance of the central nervous axis. Even if penicillin does reach the cerebrospinal fluid in rather small amounts, its concentration may not be sufficiently high to affect the more resistant bacteria. For this reason intrathecal injection is necessary for certain diseases. In equivalent antibiotic amounts, calcium penicillin is much more toxic than sodium penicillin.

The first chapters of this monograph outline in considerable detail the difficulties in producing a sufficiently high concentration of penicillin in the cerebrospinal fluid and maintaining it, together with a description of the possible neurologic sequelæ of the intrathecal use of penicillin. One important point, at least, is made clear and emphasized, namely, that intracisternal injection of penicillin is no more effective than lumbar puncture injection and that intraventricular injection of penicillin is no more effective than intracisternal, except in those rather rare cases in which a block between the ventricles and the cistern is present.

Systemically, in the treatment of lues, Herxheimer-like reactions occur with penicillin therapy in about 10% of cases. Furthermore, with the parenteral administration of penicillin, subclinical alterations in brain function may occur during the giving of the drug in somewhat more than 50% of the cases. Following intrathecal administration, meningeal reactions take place with increase in the cell count of the spinal fluid, although the protein content is not altered. Parenchymatous reactions to

the lumbar introduction of penicillin in laboratory animals consisted principally in a local radiculitis. Case histories are quoted to show that the same neurologic sequelæ occur in the human following intraspinal administration of penicillin.

Reactions are also noted following cisternal or intraventricular injections of penicillin. An occasional convulsive phenomenon is recorded in the human and in a number of instances, there have been definite changes in the electroencephalographic findings.

The direct application of penicillin to the cortex, or its injection subcortically, in the experimental animal seemed to produce convulsive attacks and electroencephalographic changes from the involved cortical areas. The neuropathologic reactions to the introduction of penicillin into the central nervous system, the authors state, show that the relatively slight reaction of the meninges and brain tissue to the local application of penicillin is in keeping with the few clinical complications following intrathecal penicillin therapy, yet an arachnitis or radiculitis may be produced by the drug. That little, if any, histologic alteration is present in the cerebral cortex, in spite of the severe convulsive effects of the drug, is not surprising, for many convulsive agents exert their effect on the brain without constant demonstrable microscopic findings.

As the first 5 chapters of this monograph appear to aim at emphasizing the bad effects of penicillin, one wonders whether the use of penicillin is justifiable. However, the second 5 chapters are devoted to the clinical results, and the potential disasters following the use of penicillin in the treatment of infections of the central nervous system are, for the most part, ignored.

The literature is carefully reviewed and very exact and detailed descriptions given of the methods for using penicillin, with or without sulfadiazine, in the treatment of meningitis, brain abscess, and other acute and chronic infection of the central nervous system. This is, to the Reviewer at least, the more interesting and valuable part of the book. The text is clear and concise; the clinical examples, well chosen and presented; so that these chapters contain a mass of information which has been skillfully made available to the profession at large. The Reviewer strongly advises every neurosurgeon to read carefully Chapters 6 to 10 in this monograph.

A final chapter is devoted to the results with streptomycin and the other newer antibiotics. With the exception of streptomycin, the other materials are so recently developed that but little information, other than from the laboratory, is available.

This is an excellent monograph, carefully prepared and well annotated, as one would expect from its senior author. The laboratory data are important in showing that, while penicillin is an extremely effective drug against certain organisms in sufficient concentration, nevertheless, its use in large amounts in the central nervous system is not without its dangers. The proper technique to be used is given in detail so that any of the unfortunate side effects, which seem to be inherent in the use of penicillin, can, for the most part, be avoided. The book is heartily recommended to all those who deal with infection in the central nervous system. F.G.

#### NEW BOOKS

*Physikalische Medizin in Diagnostik und Therapie.* By WOLFGANG HOLZER, PROF. DR. MED. ET DR. ING., Vorstand der Psychiatrisch - Neurologischen Universitätsklinik Graz. (Bücherei der Physikalischen Medizin, Band II.) Pp. 769; 379 ills. Vienna, Austria: Wilhelm Maudrich; New York: Grune & Stratton, 1947. Price, \$9.00.

*Neuropathology, Its Clinicopathologic Aspects.* By I. MARK SCHEINKER, M.D. Foreword by TRACY J. PUTNAM, M.D. Pp. 306; 208 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.75.

*Endoskopie der Harnröhre.* By DR. ALOIS GLINGAR, Facharzt für Urologie. (Weiner Beiträge zur Urologie, Band II.) Pp. 68; 36 ills. Vienna, Austria: Wilhelm Maudrich; New York: Grune & Stratton, 1947. Price, \$4.00.

*Erkrankungen des Uropoetischen Systems und der Prostata Durch Störung der Blutströmung.* By PROF. DR. KARL HUTTER. (Wiener Beiträge zur Urologie, Band I.) Pp. 200; 40 ills. Vienna, Austria: Wilhelm Maudrich; New York: Grune & Stratton, 1947. Price, \$4.00.

*Food Regulations and Compliance.* By ARTHUR D. HERRICK. Vol. 2. Pp. 655. New York: Revere Publishing Co., 1947. Price, \$10.00.

*Hospital Care in the United States.* By THE COMMISSION ON HOSPITAL CARE. Pp. 631; 94 tables; 58 charts. New York: Commonwealth Fund, 1947. Price, \$4.50. Reviewed in this issue.

*Communal Sick-Care in the German Ghetto.* By JACOB R. MARCUS, PH.D., Adolph S. Ochs Prof. of Jewish History. Pp. 335. Cincinnati: The Hebrew Union College Press, 1947. Price, \$2.50.

*Office Treatment of the Eye.* By ELIAS SELINGER, M.D., Attending Ophthalmologist, Mount Sinai, Cook County and Michael Reese Hosps. Pp. 542; 67 ills. Chicago: Year Book Publishers, 1947. Price, \$7.75.

*The Medical Writings of Anonymus Londinensis.* By W. H. S. JONES, LITT.D., F.B.A. Pp. 168. Cambridge: The University Press; New York: The Macmillan Company, 1947. Price, \$2.75.

*Dying, Apparent Death and Resuscitation.* By S. JELLINEK, M.D., Prof. of Electropathology, Univ. of Vienna, Laureat de l'Institut de France. Pp. 263. Baltimore: Williams & Wilkins, 1947. Price, \$5.50.

*Pharmaco-therapeutic Notebook.* By H. W. TOMSKI, Diploma in Biochemical Analysis. Foreword by HUGH A. DUNLOP, M.D., M.Sc., F.R.C.P. Pp. 280. Baltimore and London: Williams & Wilkins, 1947. Price, \$4.50.

*The Rotunda Hospital.* By O'DONNELL T. D. BROWN, M.B., M.A., M.A.O. (UNIV. DUB.), F.R.C.P. (I.), F.R.C.O.G. Pp. 296; 44 ills. Baltimore and London: Williams & Wilkins, 1947. Price, \$11.00.

*Nutritional Disorders of the Nervous System.* By JOHN D. SPILLANE, B.Sc., M.D. WALES), M.R.C.P. (LOND.). Foreword by GEORGE RIDDOCH, M.D., F.R.C.P. Pp. 280; 103 ills. Baltimore and London: Williams & Wilkins, 1947. Price, \$5.00.

*A Study of Individual Children's Diets.* By E. M. WIDDOWSON, B.Sc., PH.D., Medical Research Council. Special Report Series No. 257. Pp. 196. London: His Majesty's Stationery Office, 1947. Price, 6s.

A study of 1028 British children whose individual food consumption has been recorded, giving data under some 20 headings, such as calories, proteins, vitamins and so on—and on the diets of twins, diabetics, children of unemployed and their results. "The one outstanding fact, which has been brought out again and again by this investigation, is that similar individuals may differ enormously and unpredictably in their food habits."

## BOOK REVIEWS AND NOTICES

## NEW EDITIONS

*Symptoms and Signs in Clinical Medicine.* By E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Lecturer in Medicine, Univ. of Liverpool. 4th ed. Pp. 463; 346 ills., 9 in color. Baltimore and London: Williams & Wilkins, 1947. Price, \$8.00.

*Massage and Remedial Exercises in Medical and Surgical Conditions.* By NOEL M. TIDY, Sister-in-Charge, Red Cross Massage Clinic, High Wycombe. 7th ed. Pp. 480; 190 ills. Baltimore and London: Williams & Wilkins, 1947. Price, \$6.00.

*Developmental Diagnosis, Normal and Abnormal Child Development.* By ARNOLD GESELL, M.D., and CATHARINE S. AMATRUDA, M.D. 2nd ed. Pp. 496; 22 figs. New York: Paul B. Hoeber, 1947. Price, \$7.50.

*The American Illustrated Medical Dictionary.* By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S. 21st ed. Pp. 1660; 880 ills., including 233 portraits. Philadelphia and London, W. B. Saunders, 1947. Price, \$8.00 without Thumb Index; \$8.50 with Thumb Index.

*Internal Medicine in General Practice.* By ROBERT PRATT McCOMBS, B.S., M.D., F.A.C.P. 2nd ed. Pp. 741; 122 ills. Philadelphia and London: W. B. Saunders, 1947. Price, \$8.00.

*A Textbook of Pathology.* By WILLIAM BOYD, M.D., Prof. of Pathology and Bacteriology of the Univ. of Toronto. 5th ed. Pp. 1049; 500 ills.; 30 color plates. Philadelphia: Lea & Febiger, 1947. Price, \$10.00.

In the 4 years that have elapsed since the last revision, much new and important material has become available; accordingly the author has made many additions and revisions that add considerably to the textbook's value, *e. g.*, sections on the kidney in anoxia and in sulfonamide poisoning; the lung in Löffler's pneumonia. Material has been added on cardiac infarction, hypertension heart disease, the structure of the coronary arteries, and on many other topics. (M. McC.)

*An Introduction to Biochemistry.* By WILLIAM ROBERT FEARON, M.A., Sc.D., M.B., Prof. of Biochemistry, Univ. of Dublin. 3rd ed. Pp. 569. New York: Grune & Stratton, 1947. No price given.

This revised edition of a brief, elementary text, which has been quite popular in England, is well organized and readable. The subject matter appears to recommend it largely for general undergraduate courses in biochemistry. While there are practical medical applications included, phases of the subject such as gas transport, acid-base, water balance, and metabolism are not treated with the degree of detail this Reviewer would like to see in a modern text for medical students. The Bibliographies at the end of each chapter refer the reader practically solely to other texts and review articles. This device saves space and effort, but it leads to a dogmatic and compendium type of presentation. (D. D.)

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1947

## ORIGINAL ARTICLES

### A METHOD OF DETERMINING THE SITE OF RETENTION OF AEROSOLS WITHIN THE RESPIRATORY TRACT OF MAN BY THE USE OF RADIOACTIVE SODIUM\*

#### PRELIMINARY REPORT

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THE effectiveness of aerosol‡ administration in respiratory disease depends on the deposition of a maximum amount of drug at the diseased site. Two factors are of special interest: (1) the total quantity retained; (2) the pattern of distribution.

The purpose of this communication is to describe a method devised to measure the deposition of aerosols within the respiratory tract of man by means of radioactive sodium. This technique may be employed to determine the value of various methods of nebulizing therapeutic solutions.

Studies of the effectiveness of drugs administered as aerosols have progressed simultaneously in Europe, England, South

America and this country.<sup>1-6,8-12,14,16,18</sup> During the recent war, the Army and the Navy became interested in the fundamental aspects of the behavior of aerosols within the respiratory tract. Drinker, Gardner and others have studied industrial hazards, due to dust, and have investigated the deposition of finely divided particles in the respiratory tract of man and animals.<sup>6,9</sup> Studies have been made to determine the critical range of particle size below which retention is minimal and penetration to the alveoli maximal, and above which retention increases although with little penetration beyond the larynx.<sup>15,19</sup>

The retention of an aerosol within the respiratory tract is governed primarily by the size and density of the individual par-

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† Lieutenant Commander (MC), USNR, while this work was in progress.

‡ An aerosol may be defined as a suspension of finely divided particles in a gaseous medium. Steam and smoke are examples that are commonly encountered.



ticles and by the hygroscopic properties of the solution from which they are formed. Additional significant factors are the vapor pressure and temperature of the inhaled aerosol, the rate of respiration and the distribution of areas of turbulence in the respiratory passageway. The amount of the aerosol leaving the nebulizer, and the character of that aerosol, are in turn influenced by several factors—the density, viscosity and surface tension of the solution, the pressure at which the gas which is operated, the density of the gas which is used to generate the aerosol, and the design of the nebulizer. Particle size is dependent on both the nebulizer and the hygroscopic properties of the solution from which the aerosol was generated. Thus a particle of specified size when it left the nebulizer may be smaller, or larger, when it reaches the bronchus. For instance, a particle formed from a hygroscopic solution may, as it enters the warm saturated air within the respiratory tract, take on water and increase in size. Conversely, particles from a non-hygroscopic solution may become smaller. In this connection, consideration must be given to the effect of the addition to the solution of a hygroscopic substance, such as triethylene glycol, in preventing evaporation of water from the droplets in the respiratory tract. A method for the quantitative evaluation of all these factors would be valuable.

Kreuger *et al.*<sup>11</sup> have reported the use of radioactive phosphorus as a tracer for determining the site of deposition of an aerosol within the respiratory tract of a rabbit. However, since this substance emits only beta rays, which penetrate only a few mm. of tissue, it was necessary to sacrifice the animal in order to measure the deposition within the lungs. This was apparently the first instance in which radioactive material was used for this purpose.

In the present investigation, radioactive sodium ( $\text{Na}^{24}$ ), in the form of a physio-

logic solution of sodium chloride, was used as a tracer for determining roughly the pattern of deposition of aerosols within the respiratory tract of man.

The intention of this preliminary report is to describe the procedure and indicate its usefulness for comparing the deposition of aerosols in the respiratory tract under varying circumstances, and not to evaluate the techniques selected for investigation.

**Method and Results.** Since radioactive sodium emits penetrating gamma rays, its presence within tissues can be demonstrated by means of a Geiger-Müller counter placed over the site to be studied. When this material is introduced into the system orally or intravenously, it rapidly becomes diffused throughout the extracellular body fluid. It is to be expected that similar rapid distribution will result from inhalation of the material in an aerosol. Accordingly, measurements intended to show variations in amounts deposited at a particular site within the lungs would have to be made promptly after the end of the breathing period, otherwise the results might be obscured by material throughout the body.

A glass nebulizer was used to generate an aerosol of a physiologic solution of sodium chloride containing about 100  $\mu\text{c}$ . of the radioactive isotope per cc.\* The subject inhaled this aerosol for a definite period under predetermined conditions, and went immediately to a nearby room, where measurements were made with the Geiger counter placed over selected sites on his chest wall.

A series of preliminary experiments was carried out to determine the feasibility of the method, and to obtain an estimate of the variables to be considered. After the aerosol had been inhaled for a few minutes the Geiger counter placed on the chest wall in the axilla indicated a considerable deposition of radioactive material there. The value thus obtained is referred to as "chest count." These

\* details concerning the preparation of radioactive sodium, see the report of Smith and Quimby.<sup>1</sup>

counts were at a maximum immediately after the inhalation of the aerosol, decreased rapidly during the first  $\frac{1}{2}$  hour and more slowly thereafter for about 3 hours.

The maximum activity was roughly proportional to the time of inhaling, up to 15 minutes, other factors being constant. The percentage rate of decrease during the first 20 minutes was essentially the same, within the limits observed, whatever the total accumulation. This depends on the

uptake of different individuals, or of the same individual with different nebulizers or solutions, the program of breathing time and pauses should be rigidly controlled.

Since the gamma radiation from the sodium isotope is so penetrating, the question arose as to whether readings obtained at the axilla might actually be due to material near the center of the body, in the trachea, esophagus, or stomach. Accordingly, several subjects swallowed amounts

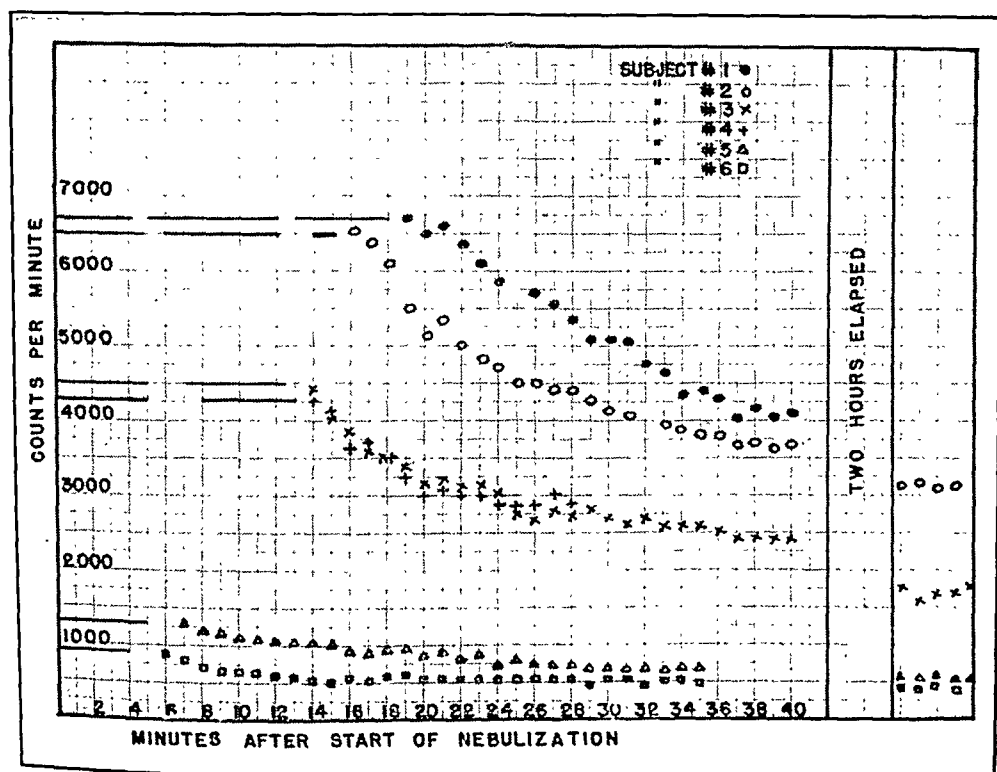


FIG. 1.—Chest counts on 6 subjects following inhalation aerosol for various times. Records start with beginning of breathing. Solid lines represent inhaling periods, breaks, rest periods, points, minute by minute counts.

passage of the sodium ions through the walls of the alveoli into the circulating blood. The count immediately after inhaling was of the order of 3 times the count after equilibrium was established. (Figure 1 shows the counts in a set of 6 individuals inhaling for approximately 5, 10 and 15 minutes. Each curve begins at the start of nebulization. The solid horizontal line indicates breathing time, the gaps showing pauses for adjustments.) It is evident that if comparisons are to be made on

of the isotope equal to those retained by the inhalers (for details of measuring retained dose, see below). In such cases the counts at the axilla were less than one-third of the count after nebulization. Evidently the larger part of the count is due to material in the lung.

Measurements made at the chest wall, alone, would be of little value. It is necessary to know the total amount of material inhaled and retained by the subject, and to correlate this with the radio-

activity measurements. Such correlations, for various conditions of inhalation with the same individuals, should give significant results. However, it is not desirable to repeat these tests too frequently on the same subjects, because of the radiation exposure. When different individuals must be used, several must be tested for each set of conditions, and the range of variations determined.

In the first tests with a group of individuals, differences were found up to 30% in chest count, per unit retained amount of radiosodium. It is possible that this can be attributed to different habits of breathing, because as individuals become more used to the procedure, the variations were less pronounced.

With groups of untrained subjects, techniques giving very marked differences in uptake would be expected to result in completely distinct sets of chest counts. Smaller differences in uptake, which might still be significant, would be likely to be overshadowed by individual variations. This is brought out in Figures 4 and 5, which are discussed below. In investigating such possible small variations, it is probable that the results of experiments on different sets of individuals might be suggestive, but that the final evaluation in a particular problem should be made by using the same set of trained subjects for the various procedures. *In this case the accompanying irradiation must be carefully evaluated.*

Determination of the amount of radioactive sodium retained by an individual can be made in the following manner: 1 of the authors (E. Q.) had previously studied counting rates at the foot ("foot counts") in a group of normal subjects, following the intravenous administration of a known amount of radioactive sodium.<sup>13,17</sup> Curves of the equilibrium build-up of radio-sodium in the extracellular fluid of the foot were obtained for a known dose of radio-sodium over a period of 24 hours. All values fell within  $\pm$  or

-15% of an average. Therefore, by taking a count at the foot of an individual at any time within 24 hours after an injection of the radioactive sodium, the amount originally administered can be determined, within these limits, allowances being made for radioactive decay. Absorption of sodium ion into the circulation takes place readily following any type of administration, and equilibrium in extracellular fluid is reached within a few hours. Therefore, readings taken at the feet of the aerosol subjects about 24 hours after the inhalation should give an approximate measure of the retained sodium. As an additional check, 11 of the subjects in this survey swallowed known amounts of the material; foot counts were then followed at intervals up to 24 hours. These agreed with those resulting from the intravenous injections. Consequently, whenever it was possible, the aerosol subject was required to return for a foot count the day after inhalation to determine the radio-sodium actually retained in his body (excretion in 24 hours is negligible).

Following these preliminary studies, experiments were conducted to investigate the practicability of comparing the pattern (site) of deposition of aerosols produced by different methods of nebulization. The apparatus used in these experiments is shown in Figure 2. Three glass nebulizers were used: a Vaponefrin\* nebulizer and 2 made by Mr. F. H. Anderson† (labelled in these experiments Anderson No. 1 and No. 2). Each nebulizer was fitted with a ground-glass joint attached perpendicularly to the outlet tube (Fig. 3). The aerosol was generated by oxygen supplied from a demand valve at a pressure of 48 to 51 p.s.i.<sup>8</sup> The "cut-off" tube of the demand valve was attached to an accessory opening in each nebulizer. The subject placed his lips around the outlet tube of the nebulizer and did not remove them during an experiment; his nose was closed by means of a clamp.

\* Designed by the Vaponefrin Company, 6812 Market Street, Upper Darby, Pa.  
† Department of Pharmacology, College of Physicians and Surgeons, Columbia University, New York.

Thus, he breathed only the oxygen which generated the aerosol and passed through the nebulizer. At the beginning of each expiration the demand valve stopped the flow of oxygen and the subject exhaled through the ground-glass joint which was connected to a tube containing calcium chloride, and it in turn to an electrostatic precipitator.<sup>7</sup> A water valve was inserted between the spirometer and the precipitator to prevent rebreathing of the exhaled aerosol. In order to eliminate excessive positive pressure during expiration, the column of water in this valve was counterbalanced to a depth of 0.5 cm. in the tube by means of an additional weight on the spirometer.

connecting glass tubes were washed into separate containers with 3 rinses of tap water. The radioactive content of these washings was subsequently measured with the Geiger-Muller counter. This determination of the amount of radioactive material left in the nebulizer and the amount exhaled furnish another measurement of the amount retained by the subject. In general the retained doses measured in this way were somewhat higher than those determined by 24 hour foot counts. This suggests that not all the exhaled material was captured.

A considerable number of experiments was made to systematize the procedure and to investigate their limitations. Two

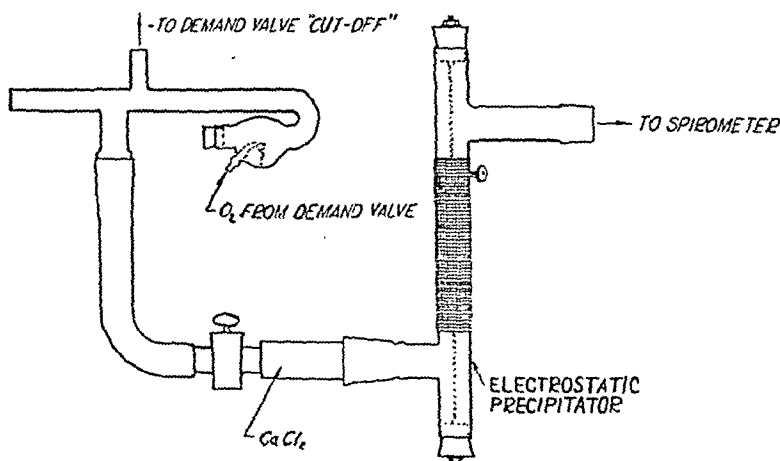


FIG. 2.—Diagram of apparatus.

A measured amount of solution containing approximately 100  $\mu$ c. of radioactive sodium per cc. of saline was placed in the nebulizer. The subject breathed an aerosol of this solution for a period of approximately 5 minutes. If the period of inhalation was to be continued he was given a rest period of from 1 to 3 minutes, during which additional solution was added to the nebulizer; this was followed by another 5 minute breathing period. Immediately following the termination of the inhalation of the aerosol, measurements were made with a Geiger-Muller counter placed in the axilla (chest counts).

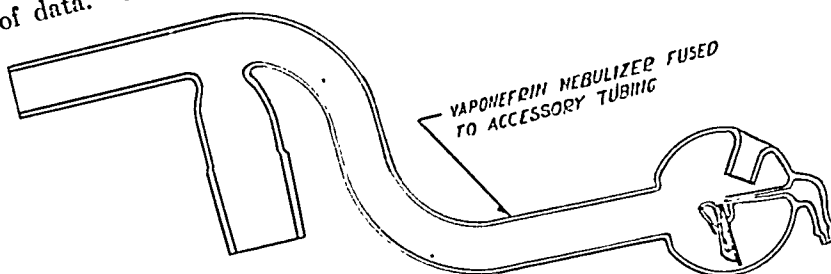
After each subject had completed a period of inhalation, the contents of the nebulizer, electrostatic precipitator and

of these are here presented as examples of the type of test which can be made. In the first, the Anderson nebulizer No. 1 was compared with the Vaponefrin nebulizer, the same solution being used in both. The second compares, with the same nebulizer, the uptake of physiologic saline solution and of a similar solution containing 10% of triethylene glycol. Each of these comparisons was made by using 3 subjects for each procedure. Accordingly, as mentioned above, it would be expected that only marked differences would be clearly shown. The results of these experiments are seen in Figures 4 and 5.

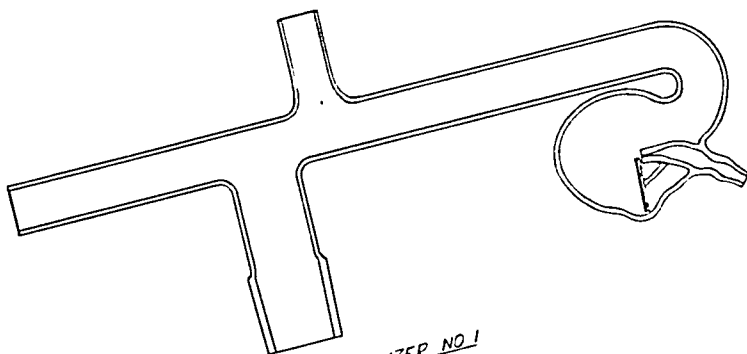
In Figure 4, the counts per unit amount retained when the Anderson nebulizer No. 1 was used appear to be, in general,

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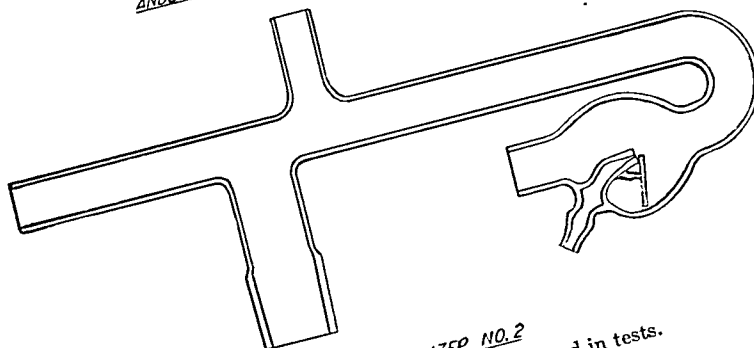
higher than those for the Vaponefrin nebulizer. However, the difference is not clear-cut; there is some overlapping of the 2 sets of data. On the other hand, separation of the 2 sets of data is definite (Fig. 5). For a given amount of material retained in the subject, the count at the chest wall was higher when glycol was



VAPONEFRIN NEBULIZER



ANDERSON NEBULIZER NO. 1



ANDERSON NEBULIZER NO. 2

FIG. 3.—Drawings of nebulizers used in tests.

when the Vaponefrin nebulizer is used throughout, half the subjects having a solution made more hygroscopic by the addition of 10% of triethylene glycol, the used. It should also be mentioned that, starting with equal amounts of radio-sodium in the nebulizers, the 3 subjects with glycol each retained considerably more

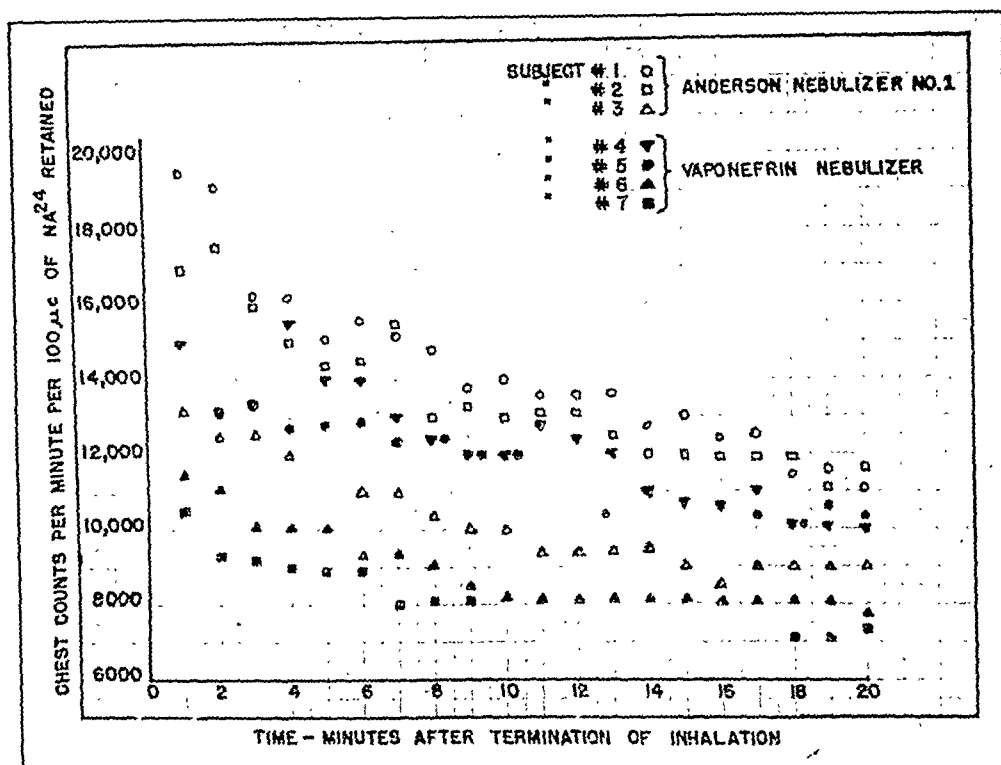


FIG. 4.—Chest counts per 100  $\mu$ c. retained  $\text{Na}^{24}$  on 7 subjects, following inhalation of aerosol for same period; 4 used on nebulizer and 3 a different one. Records start immediately after termination of inhalation. There is indication of better distribution with the Anderson nebulizer, but the difference is not clear-cut.

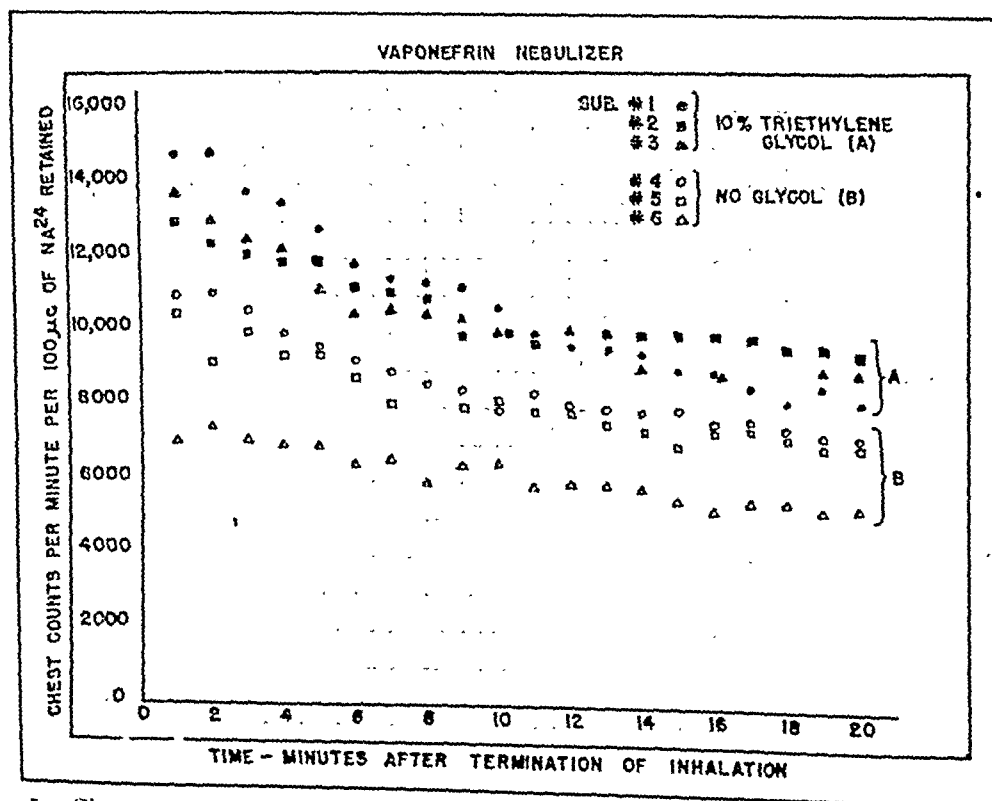


FIG. 5.—Chest counts per 100  $\mu$ c. retained  $\text{Na}^{24}$  on 6 subjects following inhalation of aerosol for same periods, 3 with and 3 without 10% triethylene glycol added to solution. Records start immediately after termination of inhalation. Addition of glycol results in greater deposition in the lung.

than those with no glycol. Thus if Figure 4 were plotted on the basis of total counts, in the same manner as Figure 1, the separation of the 2 sets of curves would be wider. On the other hand, for the 2 nebulizers of Figure 4, the amounts retained showed no systematic difference. It is not the purpose of this preliminary report to present data on various techniques, nor to outline a plan for future work, but simply to present a method for study of the deposition of aerosols within the lungs. Extensions of its use in both animal and human experiments will be evident. It is not suggested that radioactive sodium is the only suitable tracer, indeed, the most suitable for all purposes. The use of other isotopes will depend on availability, and on the particular problem under consideration.

**Summary.** In a study of the retention of aerosols within the respiratory tract, 2 factors are of special interest, the total quantity retained, and the pattern of distribution. When the aerosol is labelled by a radioactive isotope, the total quantity retained can be determined by 2 methods: (1) All material exhaled can be trapped and its radioactivity determined, as well as that of the nebulizer residue. Subtraction of these from the initial quantity gives the

amount retained. (2) When the radioisotope is a gamma-ray emitter, preliminary tests can be made to ascertain the count at the foot (or other definite position) some hours after a known amount of it has been administered orally or intravenously, when equilibrium distribution has been attained. Then by measurement at the same site on the subject, after the same interval, the amount of retained material can be calculated.

When the aerosol is labelled with a gamma-ray emitter, such as radioactive sodium, information regarding the deposition of material in different regions of the chest can be obtained by measurements made with a Geiger counter against the chest wall. Correlation of retained dose and chest count can then be made.

When inhalation technique and breathing time are carefully controlled, differences in amounts of material deposited in the lungs can be shown by differences in counter readings.

The method described should be useful in evaluating the efficiency of various methods of nebulizing therapeutic substances. By its use, differences can be demonstrated in total amount of material retained, and in amount delivered near the chest wall per unit amount retained.

The authors wish to express their appreciation for their technical assistance to the following: Mr. Max Soroka, Mr. Charles C. Rumsey, Jr., Mrs. Eva Levenson, Miss Eleanor Oshry, and Mrs. Camilla Fano, at the College of Physicians and Surgeons. Without their wholehearted coöperation, it would not have been possible to carry out this work.

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## MENINGOCOCCEMIA WITHOUT MENINGITIS

## A REVIEW OF FIVE CASES\*

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It is well recognized that war-time conditions are constantly associated with an increase in the incidence of meningococcal infections. The recent war was no exception. Although there were no extensive epidemics, there was a significant increase in the number of cases both in this country and abroad. Morbidity statistics of the United States and Great Britain for the past 10 years illustrate this fact.<sup>3</sup> The first significant increase in Great Britain was seen in 1939 and reached its peak in 1940 and 1941. On the other hand, an increase in the number of cases in the United States was not evident until 1941 and reached an all-time high level in 1943. Whereas the 5 year median (1939-1943) for the first 6 months of the year was 1211 cases, there were 2019 reported in 1942, 12,011 in 1943 and 11,841 in 1944 for the same period of the year.<sup>6†</sup>

The increased incidence of meningococcal infections has brought to the attention of the medical profession a certain number of the less obvious, but equally interesting types of this infection which may be encountered. The association of the meningococcus with an acute purulent meningitis has too frequently led to a lack of consideration of the other clinical manifestations of meningococcal infections. Although a large majority of the cases do have meningitis when first seen, a certain number will show blood stream infections

without meningitis. It is this latter group with which this paper is concerned.

Meningococcemia as a clinical entity was first described by Solomon<sup>7</sup> in 1902. Since that time a large number of cases have been reported but the condition is still considered comparatively rare. Campbell<sup>1</sup> in 1943 reviewed 88 prolonged cases collected from the American and British literature. Recently, many cases have been reported in the Australian and American journals.<sup>9</sup>

The pathogenesis of meningococcal infections is still a disputed issue. As early as 1919 Herrick<sup>2</sup> divided meningococcal sepsis into 3 stages: the localized infection in the nasopharynx, the general invasion of the blood stream, and finally the metastatic localization in the various organs of the body. Recent work seems to support this concept and as stated by Campbell<sup>1</sup> "it appears that the usual route of invasion is by the blood stream." Meningococcemia is now recognized as an entity with variable clinical manifestations. It should be appreciated, however, that not all cases showing blood stream infections proceed to localized lesions. Although some will rapidly develop meningitis or localization in other organs, others appear to subside spontaneously and still others remain for long periods of time as a bacteremia. Proper recognition is important since the disease usually responds

\* The laboratory studies on these cases were performed under the direction of Surgeon Seward E. Miller, Chief of the Laboratory Service and the Bacteriologic work was performed by Kathryn Dean, Medical Technician.

† Meningococcemia is reportable in New York State only. It is not known whether meningococcemia when reported in other areas, is included in total cases of meningococcal meningitis. Therefore, the figures given above refer to meningococcal meningitis rather than all meningococcal infections.



promptly to treatment with either the sulfonamides or penicillin.

During the past year 5 cases of meningococcemia have been observed at the U. S. Marine Hospital in Baltimore. Four of these cases were admitted within a period of 31 days and yet none of them was associated with another case of meningococcal infection or had any epidemiologic features in common. They presented variable clinical features but as a group illustrate the more common manifestations of this condition.

**Case Reports.** CASE 1. F. V. O., a 22 year old Coast Guard Seaman 1/c., was admitted June 3, 1944, with the chief complaint of headache, and vomiting of 8 hours duration. On the morning of admission the patient was awakened by a sharp bitemporal headache which persisted. In the 8 hours between the onset and admission he vomited 4 times. There was no history of chill or chilly feeling, but patient stated he felt "sick" and felt that he had a fever. Physical examination on admission to the hospital revealed a well-developed and nourished male in no acute pain or distress. Temperature was 38.4° C. (101.2° F.). The only finding was some shotty cervical lymph nodes. Initial white blood count was 13,300, with 80% neutrophils, 16% lymphocytes, 2% eosinophils and 2% monocytes. The evening following admission the patient appeared acutely ill, temperature was 39° C. (102.3° F.), he was sweating profusely and a patchy erythematous rash about 1.5 cm. in diameter which was tender to touch was noted on dorsum of hands, wrists, palms, ankles and soles of feet. He complained of pain in the knees, but no swelling or tenderness was noted. At that time a blood culture was taken which 10 days later was reported to show no growth. The following morning, in addition to the erythematous rash, there were petechiae present over ankles, feet, legs and palms. A clinical impression of meningococcemia was made. Cultures and smears were made from the skin lesions both by aspiration and scarification techniques. The smears showed a few scattered gram-negative cocci, singly and in diplo forms, morphologically similar to meningococcus. Sulfadiazine was started in the usual dosage. On June 7, 2 days after sulfadiazine was begun, the patient's temperature was

normal and he was markedly improved. By June 9, there was no evidence of a rash. Sulfonamide was discontinued on June 13 after 8 days administration. Culture from the skin lesions showed no growth. At the time of discharge, June 16, the patient was feeling well and was returned to full duty 10 days after leaving the hospital.

CASE 2. E. C. W., a 26 year old graduate nurse, was admitted June 2, 1944, complaining of headaches, fever and pain in the wrist. She was well until 2 days prior to admission when she first noted a mild sore throat associated with general malaise. These symptoms continued but she was able to remain on duty until the day of admission when she noted a severe headache and fever. The only other point of interest in the history was that the patient had been nursing a case of Rocky Mountain spotted fever for 2 weeks prior to onset of the present illness.

Physical examination on admission revealed temperature 39.2° C. (102.6° F.), pulse 140, respirations 24, blood pressure 145/80. The patient appeared acutely ill but well oriented and cooperative. There was slight congestion of conjunctivæ and the pharynx. The face was flushed and a few fine papular lesions measuring 2 to 4 mm. in diameter were seen on the forearms. There were no other significant findings.

The patient was put at bed rest and given symptomatic treatment. A blood culture was taken at this time. Sixteen hours after admission a definite skin rash was first noted over the forearms, hands, lower legs and feet. The rash consisted of 2 types of lesions: pinkish-red macules measuring 2 to 8 mm. in diameter and small punctate maculo-papular lesions, some of which had purpuric centers and a few other definitely purpuric lesions. Some of the lesions were on the palms of the hands and soles of the feet.

Because of the nature of the lesions, meningococcemia was suspected. Blood culture was repeated and an attempt made to obtain organisms from the local lesions by scarification and aspiration techniques. The material obtained by both procedures showed a few gram-negative diplococci on smear. However, on culture only the saline aspiration yielded a Group I meningococcus.

Following the findings on smears, the patient received a total of 500,000 units of penicillin over a period of 4 days and made an uneventful recovery. There was never

any evidence of meningeal involvement and although the patient complained of pain in her wrist there were no objective findings. The skin lesions cleared rapidly and had completely disappeared within 4 days.

White blood count on admission was 19,600 with 87% neutrophils. Two blood cultures taken before and 2 taken after therapy was instituted showed no growth.

CASE 3. S. B., a 48 year old Merchant Seaman, was admitted May 2, 1944, with the chief complaint of "chills." About 6 weeks before admission the patient suddenly developed a chill with no prodromal symptoms. The chill lasted 1 hour and was followed by a feeling of general bodily warmth. Following this he had chills or chilly feelings every other day except for a period of 12 days, April 1 to 12, when he was symptom-free. In spite of the chills the patient stated he felt well and was not incapacitated for work. One week before admission, while at sea, he developed a severe chill and felt sick enough to remain in his bunk. Several hours later, however, he was able to resume work. The last chill occurred 3 days before admission. At the time of admission the patient was feeling well and offered no complaint other than weakness. Physical examination was entirely negative.

On the basis of the history, blood smears for malaria were taken on admission and were reported as negative. Blood culture taken on May 4, 1944, showed no growth, but blood cultures taken on May 5, 6, 11 and 12, 1944, were reported May 15, as showing Group I meningococcus. During this interim the patient was asymptomatic and appeared to be in good health, except for a low-grade fever which reached 38° C. (100.5° F.), on 2 days. Following the report of the cultures a diagnosis of meningococcemia was made and he was started on sulfadiazine in the usual dosage. Sulfonamide therapy was continued for 1 week. Four subsequent blood cultures were reported to show no growth in 10 days. He was discharged May 26 as recovered. The patient never complained of joint pains, there were no skin lesions and no symptoms or findings suggestive of meningitis. The white blood cell count on admission was 6350 with 54% neutrophils and 46% lymphocytes. It remained at about this level throughout his

hospital stay. Other laboratory findings were not significant.

CASE 4. G. S. H., a 33 year old Merchant Seaman, was admitted on May 31, 1944, complaining of pain in the left ankle and knee. He stated that he was perfectly well until about April 15, when on board ship he noted the onset of general malaise, sore throat and fever. The following day "red and purple spots" appeared on his wrists and ankles. He remained ill for 4 days and then improved without treatment. However, he remained weak and listless until May 25, at which time he noted that his left ankle was swollen and painful on bearing weight. The following day the left knee was also swollen and painful. He was then admitted to a hospital in Philadelphia and a diagnosis of acute rheumatic fever was made. Sodium salicylate was given with partial relief of his joint pain within 36 hours. He was then transferred to this hospital for further care.

On admission, temperature was 37.2° C. (99° F.), pulse 100, respirations 22 and blood pressure 120/80. The patient appeared comfortable and was well oriented. There were no significant findings on examination. None of the joints were painful on manipulation nor showed definite evidence of inflammation. There were no skin lesions.

Following admission to the hospital the patient was kept at bed rest and observed. During the next week the patient complained of pain in other joints and the temperature gradually rose, reaching 39.4° C. (103° F.) on the 7th hospital day. Because of the patient's complaint of severe headache lumbar puncture was done at this time, but revealed no significant findings. He was started on sodium salicylate, 6 gm. per day. On the following day a rash was first noted over the lateral portions of the back, in the axillae and over the posterior aspect of the thighs. The lesions were pink macules measuring 2 x 8 mm. in diameter. All of the large joints of the extremities were extremely painful on motion though there was no demonstrable redness or swelling. The following day the laboratory reported that the blood cultures taken on June 1 showed growth of Group I meningococcus. Blood culture was repeated and smears and cultures were made from the skin lesions. The smears showed gram-negative intracellular diplococci typical of meningococcus and the

patient was started on sulfadiazine. The cultures from the lesions were subsequently reported to show Group I meningococci. The second blood culture showed no growth. The patient continued running a low grade fever and there was marked stiffness and pain on motion of most of the large joints of the body. When the joint involvement continued after 9 days on sulfadiazine therapy, penicillin was given in conjunction with the sulfadiazine for 5 days. The fever gradually subsided and both drugs were discontinued. The patient subsequently regained fairly complete motion of all of the involved joints, remained afebrile and rapidly gained strength. He was discharged from the hospital on July 17, 48 days after admission.

CASE 5. L. B. W., Jr., a 25 year old Merchant Seaman was admitted August 23, 1944, after having been seen in the Out-Patient Clinic the same day. The patient's chief complaints were chills, fever, pain in the joints and rash. He was entirely well until about 2 months before admission when, after having been swimming, his legs and arms began to ache and he experienced a chilly sensation. In the course of the next few days he had pains in several large joints of the body. Each joint remained involved for a few hours to several days. The involved joints were mildly swollen and tender and then cleared completely. Since the onset the patient had developed episodes of chilliness 3 to 4 times a week and lasting  $\frac{1}{2}$  to  $\frac{3}{4}$  of an hour, followed by development of fever and periods of profuse sweating and weakness. These symptoms continued until he was seen in this hospital. About 2 weeks prior to admission he noted development of a rash, notably on the legs and arms, never on the palms, soles, face or neck. He described the rash as "coming and going" but he did note that it seemed more pronounced following periods of fever and sweating. He also noted that the rash was tender. He had had occasional headaches for the past 2 months, but never any stiff neck.

When first seen the patient appeared comfortable, rational and had no fever. There were a few red macular lesions measuring 3 to 5 mm. in diameter over the extremities. No rash was present on the trunk. The spleen was palpable 2 fingers breadth below the left costal margin. He was admitted to the hospital with the diagnosis of chronic meningococcemia.

During his stay in the hospital he had temperature elevations on the 3rd, 5th and 6th hospital days. The temperature ranged from 39° C. (102.3° F.) to 39.7° C. (103.5° F.), but he did not appear particularly ill. The white blood count on admission was 8900, with 68% neutrophils, 28% lymphocytes, 2% monocytes and 2% eosinophils. The rash which was noted was transient in character, at times lasting only 24 hours. The lesions were pink when first seen and would rather quickly take on a yellowish-brown color and finally disappear. Blood cultures were taken and were subsequently reported positive for Group I meningococcus. Sulfadiazine was started on the 7th hospital day and thereafter there was no elevation of temperature. The patient gradually felt better and rapidly gained strength. Blood cultures taken after sulfadiazine therapy showed no growth.

The patient made an uneventful recovery and at the time of discharge from the hospital was feeling well with no complaints.

**Comment. CLINICAL MANIFESTATIONS.** Meningococcemia is a disease of protean clinical manifestations. All grades of severity from fulminating to mild subclinical types are seen. For descriptive purposes the disease may be divided into the acute and chronic types, realizing that a few cases may fall into an intermediate or subacute group.

Acute meningococcemia refers to that group of cases in which the onset is rapid and the patients are acutely and seriously sick. In some cases there is death within 8 to 24 hours after the onset of symptoms; many of these develop the Waterhouse-Friederichsen syndrome with or without hemorrhage into the adrenals.<sup>9</sup> These fulminating cases are frequently associated with purpura and ecchymotic skin manifestations. Fortunately, however, not all cases of acute meningococcemia have such a poor prognosis, as, for example, 2 of the cases herein reported. Both cases were acutely and seriously sick, but both responded dramatically after treatment had been instituted 20 and 40 hours respectively after admission.

In acute meningococcemia the onset is

usually sudden with fever and occasionally sweating and rigor. Severe pain in the joints and muscles is common, together with headaches. In the acute fulminating case, death may be rapid and the skin lesions may or may not be present. In the less fulminating cases a characteristic rash usually appears a day or 2 after onset. In the acute cases here described, Case 1 showed a pink erythematous rash, followed by petechiæ over the extremities; Case 2 showed small macules, papules and several purpuric lesions over the extremities. Both rashes appeared about 24 hours after the onset of acute symptoms. Generally, the rash is on the legs, often the arms, and less frequently on the back and trunk. In most cases the rash is easily discernible, but occasionally it will go unseen unless searched for carefully. Mitchell-Heggs<sup>4</sup> describes 4 types of skin lesions, namely: (1) small evanescent rose pink or brick red macules or papules, (2) petechiæ, (3) purpura and ecchymosis occurring in the very acute cases, and (4) herpes labialis. These may be seen separately or in combination in a single case. A somewhat characteristic feature of the rash is tenderness on pressure, as seen in 2 of our cases.

Chronic meningococccemia refers to those cases that show a less acute onset and a prolonged clinical course. The symptoms are quite variable in their intensity and character. This is exemplified by the 3 chronic cases herein reported. In Case 3 the patient's only complaint was chill or chilly feeling approximately every other day for 6 weeks prior to admission. It was only during the last week that he was incapacitated for full duty, since he felt quite well between chills. During his entire stay in the hospital he was comfortable, and his only complaint was slight malaise. In Case 4 the patient noted the onset of symptoms about 45 days before admission with the development of fever and malaise. He later developed a rash and joint pains. The rash disappeared before admission, but reappeared while in the hospital. He was weak and listless

and far more incapacitated than the other case. Case 5 had its onset about  $2\frac{1}{2}$  months prior to admission and was never completely well until after treatment with sulfadiazine.

In chronic meningococccemia the onset may be sudden with acute symptoms or the disease may begin mildly. Thereafter, some cases have been shown to subside spontaneously, others ran a low-grade active course, while others may be active only intermittently.<sup>9</sup> Generally speaking, fever, rash, arthralgia, chills and headache constitute the important features. Campbell<sup>1</sup> reviewed 88 cases of meningococccemia which showed a prolonged course and found fever present in 82, rash in 78, arthralgia in 55, chills in 48 and headache in 40.

There is nothing diagnostic about the fever in these cases as all types have been recorded, including 1 by Priest<sup>5</sup> resembling malaria.

The rash is much the same as in the acute cases, except that purpura is much less frequently seen. The rash is more frequently seen on the extensor aspects of the limbs, the back and points of pressure. The lesions may be erythematous, macular, papular, vesicular or resemble erythema nodosum and erythema multiforme. Case 3 described here showed no skin lesions after careful search. Case 4, however, showed pink macules 2 to 8 mm. in diameter over the lateral portions of the back, axillæ and over the posterior aspects of the thighs. Case 5 showed macular and purpuric skin lesions intermittently.

Arthralgia is another common symptom and was present in Case 4. Chills and headache are also frequently seen, but are of no specific diagnostic value except when associated with arthralgia and skin rash.

**LABORATORY DIAGNOSIS.** The diagnosis of meningococccemia presents an interesting and often confusing problem from the clinical standpoint. Thus it is important to resort to laboratory procedures in order to confirm clinical diagnoses and suspicions. Since treatment should not be de-

layed where meningococcemia is strongly suspected, rapid methods of diagnosis are especially valuable. A great deal of attention has been focused recently upon the diagnosis of this condition by smears of the skin lesions.<sup>8</sup>

In this group of cases bacteriologic studies of the skin lesions were divided into 2 types: (1) scarification and (2) aspiration. The scarification technique has been recently described by Tompkins<sup>8</sup> and consists essentially of the same steps which are commonly used in the preparation of a suspected syphilitic lesion for darkfield study. In the aspiration technique, the skin over the lesion was prepared with alcohol. With a tight, auto-claved syringe and hypodermic needle about 0.1 cc. of normal saline was injected into the lesion, the point of the needle was moved about within the lesion in order to produce some tissue maceration, and as much fluid as possible was aspirated. The fluid obtained on aspiration and the tissue fluid obtained by scarification was cultured and smeared on slides. After fixation in methanol the smears were stained with Giemsa and Gram's stains and studied immediately. Smears showing intracellular diplococci morphologically consistent with the meningococci were considered positive.

One of the cases had no skin lesions but showed a positive blood culture on 4 separate occasions. Only 1 other case showed meningococcus on repeated blood cultures despite the fact that there was clinical evidence of an active bacteremia. Of the 3 cases with skin lesions, all had positive smears and 2 showed growth of Group I meningococcus on culture of the material obtained by scarification and/or aspiration.

It is our impression from this group of cases that blood cultures, and smears and cultures of material from skin lesions affords the highest percentage of laboratory diagnoses. Other workers have reported results similar to those obtained in this series on blood cultures. The bacteremia appears to be an intermittent

finding, even in acute cases showing the typical clinical picture of meningococcemia. Therefore, the value of a negative blood culture in an individual case is principally of academic nature and is not strong evidence against meningococcemia. Too, the fact that growth on blood culture is often delayed for several days decreases its value in the handling of a suspected case. To delay therapy until the blood culture is reported would, of course, be disastrous to many patients with meningococcal infections. It is of special value to have some laboratory confirmation, which is quite accurate, in the early stages of this disease. Smears of the skin lesions seems to fulfill this need. The culture of material from these lesions is of interest but is of added value only in the same manner as blood culture studies. Such cultures afford late confirmatory evidence in a fairly large percentage of the cases. Since all of these procedures are easily performed and may supply some further information, it is felt that they should be done routinely in all cases of suspected meningococcemia.

**Treatment.** The treatment of these cases adds nothing to the information already present in the literature on this subject. The meningococcemia has been shown to respond to sulfonamide therapy in almost every instance. Recent evidence indicates that penicillin is probably as effective as the sulfonamides and possibly more effective. Three of these cases responded promptly and satisfactorily to sulfadiazine. Another responded to penicillin. The fifth case was apparently cleared of his bacteremia with sulfadiazine but because of the slow response of the arthritis penicillin was administered later in conjunction with the sulfadiazine. It was not felt that penicillin hastened the recovery of this case.

**Summary.** 1. Five cases of meningococcemia, 2 acute and 3 chronic, are reported and the case histories are reviewed with reference to previously reported findings.

2. The importance of laboratory studies in the diagnosis of meningococcemia is emphasized. Bacteriologic study of the skin lesions was found to offer a valuable rapid diagnostic method in suspected cases of meningococcemia.

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## STUDIES IN EPILEPSY

## EXPERIMENTAL INDUCTION OF GRAND MAL SEIZURE DURING THE HYPNOIDAL STATE INDUCED BY SODIUM AMYTAL

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THE relationship between epilepsy and aggressive urges has been frequently discussed.<sup>2,3,6,8,10,11</sup> Hamill<sup>7</sup> induced facial expressions of rage during attacks of *petit mal* by tapping the patients lightly on the face. Bartemeier called attention to the common use of some components of the major fit in expression of anger.<sup>3</sup> Barker has observed that convulsions, minor fits and equivalents occurred in rage-provoking situations in which the subject found it unacceptable either to experience or to express the emotion. He interpreted these fits as mechanisms which blocked consciousness of or expression of aggression.<sup>1</sup>

Intravenously administered sodium amytal has been used in the study of other disorders as an aid in the understanding of the pathogenesis of symptoms. Symptoms of asthma, hypertension, peptic ulcer and other syndromes have been precipitated or intensified during discussion of significant problems and abolished or diminished during reassurance.<sup>12</sup> Thus, the relevance of certain situations and conflicts to disordered bodily functioning has been established. The present communication reports the observation of an experimentally induced major convulsion as the subject abreacted violent rage. This rage had previously been repressed and was a significant factor in the development of his illness. A detailed psychologic study of this patient is presented elsewhere.<sup>1</sup>

**Case Report.** A 26 year old married machinist was discharged from the Navy in

1944 with the diagnosis of "Epilepsy." He has also had frequent migraine headaches since the age of 8 and epigastric pain for nearly 2 years. Roentgen ray studies in November 1946 revealed a peptic ulcer. The chief complaints relating to the present illness were psychomotor seizures since the age of 16 and major convulsions since the age of 24. The details of the history, given here in sequence, were obtained in several interviews, some with the aid of sodium amytal and hypnosis.

The subject's mother had had "sick headaches" but no relative is known to have had convulsions. He was the youngest, and is the only living, of 4 children born to the mother in her first marriage. The other children died in infancy of causes unknown to the patient. The patient knew nothing of the character of his real father until his entrance into military service required consultation of official records. He then learned, he says, that his father had been imprisoned for "assault" and "robbery" and was apparently a "criminal type."

The mother divorced her first husband shortly after the patient's birth and immediately remarried. She was a cold, irritable, domineering woman, alternately solicitous and abusive. A half-sister, aged 12, is the only child of the second marriage. The patient was adopted in his first year by the step-father and was given his name at the age of 6. The latter was friendly and a good companion, but he was occasionally cruel to the patient in sudden outbursts of rage. For example, when the patient was 8 he was one day "eating bits of food from father's plate" when the father, in a burst of anger, picked up the plate and broke it over the patient's head. Shortly thereafter head-

aches began. These were attributed to "sinusitis."

The patient's birth and early development were not remarkable. He was circumcised at 18 months. He bit his nails until he was 12 and had frequent temper tantrums when frustrated by his mother, until he was 6 years old. They were terminated one day when he was very demanding for a toy and she slapped him so hard that some front teeth were dislodged. With the termination of his temper tantrums his attitude toward his mother changed. Previously warm and affectionate, he became hostile and suspicious in response to her alternately friendly and rejecting behavior.

In addition to the headaches referred to above, he had occasional "stomach upsets" in late childhood. After an attack of abdominal pain, during his 12th year, an appendectomy was done. He did well in school work until he quit in the 3rd year of high school at the age of 16. His father was ill at the time with recurrent "pneumonia" and the patient went to work to help support the family.

The onset of psychomotor seizures at 16 was associated with the following sequence of events. In February 1936, because of headaches, he underwent an operation for drainage of the maxillary sinuses which, however, failed to relieve the headaches. In May of that year he was struck by a hard-driven baseball over the right eye and was "dazed" for about 6 hours. Shortly thereafter he had to quit school. In June, while "feeling big enough to get by with it," he refused to do an errand. This act of defiance led to a violent quarrel with his father. The latter, while angry, struck the patient several hard blows with his fists. Under sodium amytal, he revealed the murderous wishes this fight aroused but which he was, because of his father's demonstrated physical superiority, unable to act on. A feeling of helplessness and impotence resulted. Immediately after this fight the father, feeling regret, discussed their relationship in a friendly manner and revealed that he had adopted the patient and had tried to treat him as his own son. The patient was deeply depressed by this news and some days later, while playing baseball, suddenly quit the game without explanation, walked home in a daze, and went to sleep.

He awakened 2 hours later with complete amnesia for the episode.

At monthly or bimonthly intervals for the next 3 years, he had similar seizures of dazed, "automatic" behavior, lasting 30 to 90 minutes, followed by amnesia. Headaches of the migraine type occurred at about the same frequency. One-sided facial tingling and scotomata which preceded the headaches also often immediately preceded the psychomotor spells. On rare occasions psychomotor attacks occurred during migraine headache.

The first complete loss of consciousness occurred in January 1939, 3 years after onset of psychomotor seizures. His father had been in bed for 2 days with a "chest cold." The patient came home from work on the 3rd day to find his father alone in the house and critically ill with pneumonia while his mother was at court involved in a minor litigation. He hurried to the court to get her. When he saw his mother he suddenly became enraged, rushed at her, and grasped her by the throat. The "lights suddenly began to go around and around" and he lost consciousness. His father died a few days later. The patient has never forgiven his mother for her "neglect" which he feels was responsible for his father's death.

For 6 months after this event, the patient was daily confused, depressed and irritable. Psychomotor attacks occurred at least once each day. In August of that year, against his mother's wishes, he married a girl whom he had known for a few months, who "made me feel good." His attacks then became of shorter duration and occurred once each month. However, marked dizziness was now associated with the spells. He continued to work at the same job for the next few years and had been twice promoted when he entered the Navy in the summer of 1943.

During his first 6 months in the Navy he had only 2 brief psychomotor spells. Then in September 1943, a few days after his convoy was under heavy attack, he suddenly lost consciousness. He was hospitalized on arrival in England whence he was returned to the United States. After several weeks of hospitalization and study, he was discharged from the service in April 1944, because of his disability.

He had his first known major convulsion



shortly thereafter during an argument with an overbearing truck driver. He has had approximately 15 major fits since that time, usually occurring promptly during situations provocative of intense anger. Psychomotor seizures, on the other hand, occurred more characteristically 2 or 3 days after unsuccessful attempts to forget episodes of anger.

In 1945 the patient lost his steady job because of his fits. It became necessary for his wife to go to work to support the family. He soon began to have epigastric pain occurring 1 hour or 2 after meals and relieved by food taking. The patient, forced to work thereafter at odd jobs, became increasingly frustrated and angry. In this setting his fits became more frequent and his epigastric pain more troublesome. He was hospitalized in November 1946 and Roentgen ray revealed an ulcer. Gastro-intestinal symptoms were successfully alleviated by January 1947 and the ulcer had disappeared.

Examination revealed the patient to be a short, stocky, young, white male in good physical condition. He displayed some blocking of thought, numerous adventitious movements of the skeletal and facial muscles and he appeared tense and depressed. He spoke in a low-pitched, flat voice and stuttered intermittently. He seemed of above average intelligence. He was courteous in manner, well oriented, conscious of his mood and mental state, and seemed to be well motivated in seeking help for his difficulties. Examination of motor and sensory functions revealed no abnormal signs. Laboratory studies showed an abnormal electroencephalogram with low voltage fast and 7 per second waves in all leads. An outburst of large, slow waves of the psychomotor type occurred during hyperventilation. Electroencephalograms in a military hospital in 1944 were also abnormal. Two oral glucose tolerance tests were abnormal, with blood sugars at the 3rd hour falling to 49 and 59 mg. per 100 cc. respectively.

**OBSERVATION.** The patient was placed in a semi-reclining position and needle electrodes were placed for monopolar recording on the 6 channel electroencephalograph. A control record was obtained. It was abnormal, though less so than in previous tests, in that slow waves were less frequent and the response to over-

breathing was essentially normal. After a short rest, intravenous injection of sodium amytal was begun at the rate of 1 cc. of a 10% solution per minute.

The immediate relaxation induced in most patients during sodium amytal injection was in this case transitory. The patient shortly began to display, in face and posture, evidence of tension. Asked "What is the matter?" he replied, "My m-m-m-mother." The patient stuttered, spoke in a low flat voice, and the attitude of tension increased. He began to grimace and to mutter over and over, "Oh, oh, oh."

He was asked, "How does your mother bother you?" After a few seconds he said, in a tense, ominous tone, "I wish I could get ahold of her. I'd k-k-k-k-kill her." He continued to speak of his mother, saying, "She's no good. She's always bothering me. All the time. All the time." During these speeches his face acquired an increasingly angry expression and his voice became more and more hostile and threatening. "My mother killed my father," he continued. "I'll kill her some time. She drives me crazy." His teeth were bared, his voice snarling, and his attitude was expressive of violent hatred.

The tempo of this state of rage had rapidly increased. He raised both clenched fists to his forehead and appeared no longer able to express the increasing intensity of emotion. Three minutes had passed, 0.3 gm. of sodium amytal had been given, and injection was stopped. Breathing during this period was not unusually accentuated.

At this point the writing pens of the electroencephalograph were vibrating at full amplitude. Suddenly the subject's expression became blank, he gave a short inspiring strident "cry," and appeared to be in the tonic spasm of a major seizure. Clonic movement-then occurred in rhythmic fashion and the patient in one burst kicked a hole in the wall of the room. There was no incontinence and he did not bite his tongue.

At the moment that the expression became blank the electroencephalograph began to record seizure patterns. The convulsion lasted for about 2 minutes and was followed by stupor for 4 minutes, from which the patient recovered and the inter-

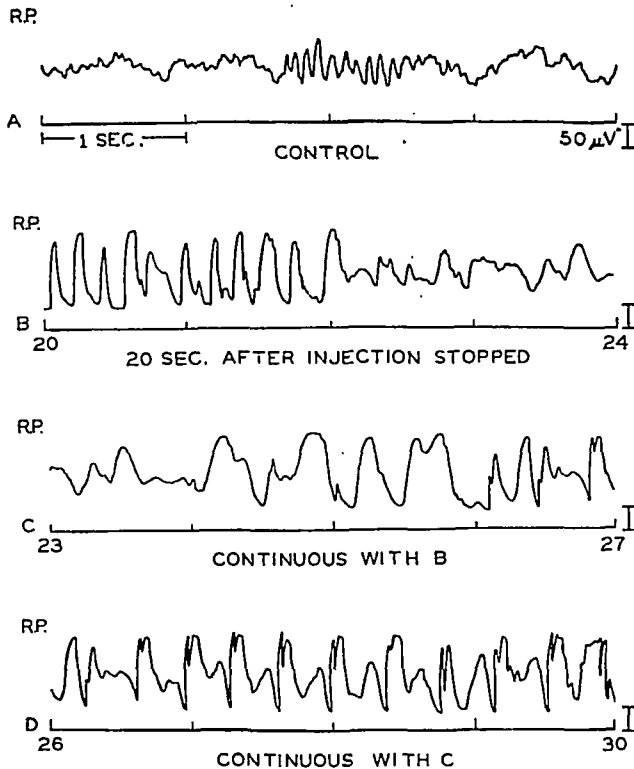


FIG. 1.—EEG wave patterns during development of a major convulsion during sodium amytal interview. Monopolar recording through the 6-channel Grass machine. All illustrations from the right parietal lead with the usual amplification and filtering constant throughout. *A*, Control record before amytal was given. *B*, As the reaction passed from rage into the tonic phase of the convulsion. *C*, Overlapping continuation of *B*, showing the transition to *D*, end of the tonic phase with wave pattern similar to that described by Gibbs as "grand mal with petit mal component seizure."

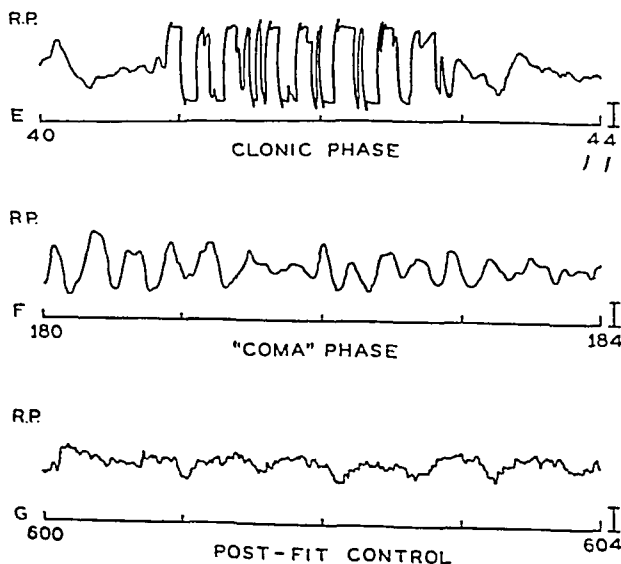


FIG. 2.—EEG during the further development of the convulsion shown in Figure 1. *E*, A clonic burst 41 seconds after the convulsion began. The high voltages threw the writing pens into the stops, producing the squared waves. *F*, Postconvulsive coma 3 minutes after the fit began. *G*, Ten minutes after the fit began and 6 minutes after recovery of consciousness. The absence of fast activity usually associated with the intravenous administration of sodium amytal is interesting.

view was continued. The stages of the fit as recorded in the electroencephalograph are shown in Figures 1 and 2.

**Discussion.** The value of sodium amytal interview as an aid in establishing a connection between situational conflict and the symptoms of "epilepsy" is indicated by this experiment.

In the patient's life situation, symptoms ensued whenever he was unable fully to feel or express aroused anger. Major convulsions occurred when rage began to break through inhibitory restraints. Psychomotor seizures occurred when anger, perhaps modified by the delay, finally broke through the temporarily effective inhibition which had held it suppressed for 2 or 3 days.

In the experiment, aggression increased exponentially as if restrictions had been removed. The rapidly mounting rage reaction was suddenly superseded by a major convulsion when the rage became uncontrollably intense and destructive action seemed imminent. It appeared that the fit deflected the murderous drive from its socially unacceptable goal and allowed its discharge as undirected energy. Thus, with the onset of the fit, his frankly menacing attitude, verbal threats and hostile behavior were abruptly succeeded by blankness of facial expression, silence, unconsciousness and convulsion.

The inhibitory influences opposing aggressive drives are presumably contained in the function of the cerebral cortex, particularly of the frontal lobes. And in general, the behavior of persons to whom

sodium amytal has been administered may be described as "uninhibited." Wolff and Gantt<sup>13</sup> have reported a phase, occurring shortly after the injection of comparable amounts of barbiturate, in which conditioned reflex response is briefly but significantly augmented. The studies of Himwich and his group<sup>5,9</sup> indicate that the frontal cortex is the first to be affected during the administration of the barbiturates. Diethelm<sup>4</sup> observed incidentally the occurrence of major convulsions shortly after the induction of hypnosis but made no comment on the mechanisms by which they were produced. It is suggested that the violence of this subject's reaction resulted from the inactivation by sodium amytal of cortical inhibitory influences and subsequent mobilization and liberation of repressed emotion.

The subject was closely observed by both authors during the experiment and neither excessive hyperventilation nor Valsalva-like maneuvers were noted.

**Summary and Conclusions.** It has been possible to produce in an "epileptic" patient, under light sodium amytal narcosis, during abreaction of a relevant conflict, an attack of *grand mal*, clinically and electroencephalographically characteristic. The attack culminated and interrupted an increasingly violent and intense state of rage. The sequence of events suggests that the fit constituted a resolution of the conflict between uncontrollable rage and the restrictions of conscience and society.

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## MENTAL DEFICIENCY OF PRENATAL ORIGIN: A CHALLENGE TO PREVENTIVE MEDICINE\*

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DURING the past few years research in several seemingly unrelated fields has revealed a number of possible prenatal causes of mental deficiency. The present brief review of this work is intended to show how much information has accumulated which, if further investigated, may offer practical means of prevention of a significant proportion of all cases of mental deficiency. The great importance of the problem under consideration is apparent from Benda's<sup>8</sup> data, which show that 2 to 4% of the population have some degree of subnormal mental development, and that the cause of idiocy is antenatal in 50%, and that of imbecility in 40% of all cases. Benda<sup>9</sup> also states that 30 to 40% of the severe cases of mental deficiency arise in families who could expect normal offspring. The distribution of some of the important types of feeble-mindedness is shown by Benda's<sup>10</sup> review of 200 autopsies. These included, among others, 50 cases of mongolism, 19 microcephalics, 13 hydrocephalics, 5 instances of congenital syphilis, 2 of Kernicterus, 20 familial morons and high-grade imbeciles and 15 endogenous idiots and low-grade imbeciles.

In addition to feeble-mindedness of strictly prenatal origin, mention will be made of mental defects which are caused at the time of birth, as well as certain forms of blindness and deaf-mutism. The latter conditions are related to mental deficiency not only because they, too, confine many patients to institutions, but

also because their causes are often strikingly similar to those of feeble-mindedness. The conditions to be discussed, and the principal pathologic changes associated with them, are compiled in Table 1.

Much of the work to be reviewed has been reported only recently and cannot be fully evaluated at this time. Various reports will therefore be taken at their face value, to serve as leads for further work.

Numerous hereditary traits produce mental deficiency, with or without conspicuous gross malformations.<sup>32,59,61</sup> Their prevention is obviously a matter of eugenics, and can only be carried out with promise of success when it is based on knowledge of the genetics of the trait in question. Snyder<sup>60</sup> has reviewed the factors to be considered in the genetic analysis of a trait, and pointed out some of the mistakes commonly made in investigations of this kind. In view of the rarity of some of the traits to be examined, a coördinated nationwide effort may be necessary in order to obtain statistically significant information. American advocates of eugenics recommend voluntary measures, often only in the form of informing prospective parents about the probability of having abnormal offspring. To draw the proper conclusions from such information, requires on the part of those being advised a level of intelligence and coöperation which may be lacking, particularly among persons with low-grade feeble-mindedness who are not confined to institutions.

\* The material presented in this article was gathered in the course of a more extensive review of mechanisms of abnormal development.<sup>30</sup> It was felt that the subject should be presented separately and in more detail, in order to call attention to the large volume of information of potential medical significance which has become available during the past few years. It is obvious that no one can be an expert in all of the special fields upon which this compilation has touched. For this reason the author has largely refrained from a critical discussion, and has limited himself to gathering data which may be stimulating and valuable to workers in the various specialties concerned.

TABLE 1.—PRENATAL CAUSES OF MENTAL DEFICIENCY, BLINDNESS AND DEAF-MUTISM

Cause	Principal pathologic change in				Other abnormalities
	Brain	Eyes	Ears	Various types	
Hereditary defects	Various types	Various types	Various types	Various types	Various types
Fetal infection:					
Syphilis	Meningovascular inflammation	Keratitis, iridocyclitis, chorioretinitis, atrophy of optic nerve	Extension from meningitis, gummas, labyrinthitis	Inflammatory changes in viscera, bones, skin	Inflammatory changes in viscera, bones, skin
Toxoplasmosis	Encephalitis, hydrocephalus	Chorioretinitis	....	Inflammatory changes in viscera, muscles	Inflammatory changes in viscera, muscles
Rubella	Microcephaly	Cataract, glaucoma, microphthalmia	Defective differentiation of inner ear	Malformations of heart, teeth; retarded development	Malformations of heart, teeth; retarded development
Fetal deficiency:					
Iodine: cretinism	Morphology poorly understood	Occasionally cataract	Hyperostosis of bony labyrinth	Changes in skin, general development, thyroid	Changes in skin, general development, thyroid
Pituitary: mongolism*	Atrophy of cortex, defective myelinization	Occasionally cataract	....	Malformations of skeleton, heart; retarded development	Malformations of skeleton, heart; retarded development
Oxygen	Necrosis, hemorrhage	....	....	Aspiration of vernix; occasionally congenital pneumonia	Aspiration of vernix; occasionally congenital pneumonia
Blood group incompatibility	Kernicterus	....	....	Erythroblastosis, icterus gravis hydrops fetalis	Erythroblastosis, icterus gravis hydrops fetalis
Malformations of unknown origin	Various kinds	Various kinds	Various kinds	Various kinds	Various kinds
Birth injury: Mechanical	Hemorrhage, necrosis	....	....	Trauma to viscera, skeleton	Trauma to viscera, skeleton
Anoxia	Necrosis, hemorrhage	....	....	Massive aspiration of vernix, and meconium	Massive aspiration of vernix, and meconium

\* According to Benda and co-workers.<sup>12</sup> Other suggested causes of mongolism are mentioned in the text.

Gamble<sup>27</sup> recently reported on sterilization of the mentally deficient which is now provided in 24 states. Eugenics also presents problems other than medical, which will not be discussed here.

Among fetal infections capable of producing lesions leading to defects of mental development, eye sight or hearing, syphilis has long been recognized and extensively studied. The method of its prevention, namely, antisyphilitic treatment of the mother, has been widely adopted and has resulted in a diminution of the frequency of congenital syphilis. The problems involved in this treatment, and much information concerning incidence and prognosis of treated and untreated congenital syphilis, have been gathered by Moore.<sup>47</sup> According to figures quoted by Moore, 64.5% of the infants of untreated syphilitic mothers are infected *in utero*. Of these, about 5% develop neurosyphilis; eye lesions are found in about 1% of early cases, and in 30 to 55% of late cases. Deafness occurs in 1.8 (13.6%) of late cases, according to 2 sources quoted by Moore. Dayton<sup>21</sup> found in a large series of mentally defective inmates of institutions that in 1.7% of all cases the cause was presumably congenital syphilis. It is concluded that syphilis is a "negligible factor" in the causation of mental deficiency. Education of the public, prenatal examination and care, and effective antisyphilitic treatment have contributed to a reduction in the incidence of congenital syphilis. In 1946, 32 states in this country required a negative serologic test for syphilis from both applicants for a marriage license. Despite progress in the control of this problem, there are still considerable numbers of infants born in our time with manifest or hidden syphilitic infection. The pathology of the lesions in the brain does not differ essentially from that in syphilis acquired after birth; meningitis, vascular lesions, degenerative changes, or gummas may occur. Eye changes include iridocyclitis, keratitis, chorioretinitis and atrophy of the optic nerve.<sup>23</sup> Lesions in the ear have been reported by Mayer<sup>43</sup>

and by Mayer and Fraser.<sup>44</sup> Mayer assumes an extension from syphilitic meningitis to the acoustic nerve and labyrinth. Mayer and Fraser describe gummatous osteomyelitis and periostitis, serous labyrinthitis and gummas in the ganglion spirale. Changes in the viscera, skeleton and skin are described in textbooks of pathology.

Our knowledge of congenital toxoplasmosis and its cerebral and ocular manifestations is relatively recent. It appears that many persons carry toxoplasma without untoward effects, but transmission from the mother to the fetus may lead to severe changes, including encephalitis, hydrocephalus, chorioretinitis and visceral lesions.<sup>13,19,77</sup> Obviously, further research must endeavor to determine toxoplasma carriers in man and animals, and find means to prevent or combat infection. Morphologic recognition of toxoplasma carriers offers considerable difficulties even at autopsy.<sup>54</sup> Immunologic methods were recently used in a family with 1 affected member, and revealed positive reactions in 10 of 11 persons tested.<sup>1</sup>

Since the first report by Gregg in 1941,<sup>29</sup> a large number of workers have described malformations which develop if the mother contracted certain virus diseases, usually rubella, during the early months of pregnancy. Articles by Swan,<sup>66</sup> Albaugh<sup>2</sup> and Aycock and Ingalls<sup>3</sup> will serve to introduce the reader to the rapidly growing literature on this subject.

Included are, among other abnormalities, mental deficiency, deaf-mutism and blindness, occurring in various combinations. The number of cases on record suggests a high incidence of maldevelopment, and some authors<sup>55,68</sup> believe that it is close to 100% if rubella occurs during the 1st or 2nd month of pregnancy. On the other hand, Fox and Bortin<sup>26</sup> found many cases without malformations in epidemics in Milwaukee. It is obviously more difficult to find these negative cases than those with malformations. The virus may not be identical in all instances; and carry a different pathogenicity for

the fetus in various epidemics.<sup>29,55,67,68</sup> Conte, McCammon and Christie<sup>17</sup> examined a series of cases with malformations resembling those known to follow maternal rubella. They obtained a history of rubella during pregnancy from 5 of 61 mothers who answered their questionnaire. This is a high percentage, particularly in a group that includes mongolism and hydrocephalus, which probably have other causes in the majority of cases. In a similar survey reported by Hopkins,<sup>33</sup> 10 of 116 mothers gave a history of rubella and 2 of influenza. Even though abnormalities may not occur in all cases with rubella during the early months of pregnancy, they are certainly sufficiently frequent to demand preventive measures aimed at the control of rubella during the child-bearing age. The interruption of pregnancies complicated by rubella during the first trimester as taken into consideration by several authors,<sup>2,3,20,55,67</sup> is at best a temporary expedient, to be employed until a true preventive measure is found. Even now the objection may be raised that the high incidence of malformations following rubella has not been proved beyond doubt.<sup>24,26</sup>

It is not known whether the fetus itself is infected with rubella, or suffers from sequelæ of changes in the maternal organism. The pathology of the brain has not been reported. In many cases there is microcephaly; very recently the occurrence of mongolism has been found.<sup>36</sup> Eye malformations include cataract of a specific type, microphthalmia, and congenital glaucoma. The histologic appearance of the cataract in infants has been described by Swan.<sup>65</sup> Two reports deal with presumed early stages of eye lesions. One<sup>18</sup> describes changes in the lens of a 2 month embryo which may well be insignificant artefacts. The other one<sup>66</sup> reports in an early embryo unilateral microphthalmia with changes of such severe degree that they could hardly have gone on to the types of microphthalmia usually seen in affected children. The inner ear has been examined only in 1 case; it showed defec-

tive differentiation of the labyrinth.<sup>14</sup> In the viscera, heart malformations occur and have been identified in some cases as patent ductus arteriosus and interventricular septum.<sup>65</sup> Microscopic examination of various organs of 3 infants revealed no definitely significant abnormalities.<sup>65</sup> Obviously, additional autopsy findings in embryos and infants are needed.

Endemic cretinism has long been recognized as a sequel of a deficiency of thyroid hormone or iodine in the maternal environment of the fetus. Associated deaf-mutism occurs in the same endemic areas.<sup>64,70</sup> The problems of cretinism have been discussed by Nobel, Kornfeld and Ronald,<sup>52</sup> Benda,<sup>11</sup> and very recently by Hurxthal and Musulin.<sup>34</sup> The latter authors have shown that many possible causes must be considered, and that the problem of the origin of cretinism is far from solved. There are not only various environmental factors to be taken into consideration, but also intrinsic ones, such as a hereditary inability to use iodine to the full extent.<sup>52,61</sup> Mental deficiency of cretins often fails to respond satisfactorily to hormone therapy. It is therefore believed that this defect is either caused by thyroid deficiency at a very early prenatal age, or coördinated to the hormonal defect rather than caused by it. In the opinion of many authorities the preventive use of iodine in the diet in endemic areas has greatly reduced the incidence of cretinism. Wespi<sup>70</sup> finds that in Switzerland the decrease in the incidence of deaf-mutism is in direct proportion to the increased use of iodized salt in the diet. The pathologic changes in the brain are not well known.<sup>11</sup> In the inner ear hyperostosis of the bony labyrinth has been observed.<sup>4</sup>

A maternal pituitary deficiency, not clearly defined in its mechanism, is believed by Benda, Dayton and Prouty<sup>12</sup> to be the cause of mongolism. This theory is based on pathologic findings in various parts of the body. Beidleman<sup>6</sup> supports this view. Other investigators<sup>24,45</sup> accuse an abnormal uterine environment of the fetus, and mention in support of this theory the fre-

quent history of a preceding abortion. Still others<sup>31,38,61</sup> find indications of some genetic factor involved. Southwick<sup>63</sup> suggests that an intragametic, non-chromosomal factor causes mongolism. Even if there is pituitary deficiency, and if the diagnosis can be made in the newborn, the question remains whether substitution therapy after birth will be effective. It seems more desirable to recognize and eliminate the condition in the mother before it affects the fetus. An extensive review of the subject, favoring the theory of pituitary deficiency, has been given by Benda<sup>11</sup> and criticized by Macklin and Snyder.<sup>41</sup> Ingalls<sup>35</sup> has recently reviewed the various manifestations of mongolism, and the existing theories dealing with their cause. He concluded that none of these theories explain satisfactorily all known features of mongolism. It is stated that many of the relatively frequent concomitant malformations originate during the 6th to 9th week of fetal life, and that a cause acting at that time or earlier should be sought for. One might add to Ingalls' considerations that not all cases of a given syndrome of developmental abnormalities must necessarily have the same cause. It has been found that widely different factors, even genetic and extrinsic ones, may have a very similar effect, probably by acting upon the embryo at a stage when a definite pattern of sensitivity of various parts exists.<sup>30</sup> As to the time of origin of abnormalities, the old practice of determining it from data of normal descriptive embryology (*teratogenetische Terminationsperiode* of the old teratologists) is very unreliable in many instances. We have learned during recent years that mechanisms of maldevelopment differ so widely (including even secondary degeneration) that they cannot possibly be determined by speculation.<sup>30</sup>

The inconspicuous pathologic changes in the brain in mongolism have been described by Benda.<sup>7,11</sup> A peculiar type of cataract occurring occasionally in mongolism and cretinism is on record.<sup>23</sup> A large variety of other malformations fre-

quently associated with mongolism have been discussed by Ingalls. As an example of these, septal defects in the heart may be mentioned; they were found at autopsy in 22 of 30 cases.<sup>35</sup>

Fetal oxygen deficiency as a cause of brain damage and subsequent mental defect has been studied by several investigators in infants<sup>15,39,57</sup> and in experimental animals.<sup>72,73</sup> It occurs most commonly during labor, but it may also happen earlier, as is indicated by yellow stained vernix of some newborns who are not icteric. This stain is due to meconium, discharged into the amniotic cavity during an episode of anoxia some time before birth.<sup>16</sup> In guinea pigs, controlled periods of anoxia at birth produce morphologic changes in the brain, and abnormalities of behavior which, if not severe, are comparable with human mental deficiency.<sup>72,73</sup> In human cases it is difficult to decide whether brain damage is the cause or the sequel of anoxia, but there are good indications that in some cases the cerebral changes are produced by anoxia.<sup>39,57</sup> Proper prenatal and obstetrical care should reduce anoxia of the fetus to a low minimum. In certain cases, maternal and consecutive fetal anoxia should be combated by the administration of oxygen to the mother.<sup>5</sup>

When Levine and co-workers<sup>40</sup> discovered that erythroblastosis fetalis is caused by maternal antibodies transmitted to the fetus (usually if the fetus is Rh-positive and the mother Rh-negative), it became apparent that Kernicterus and the associated functional disturbances are also caused by this blood group incompatibility in the majority of cases.<sup>22,69,75</sup> Only recently a statistical evaluation of blood group examination in mentally defective children and their mothers suggested that milder forms, which do not have the typical Kernicterus sequelae or a history of erythroblastosis, may also be due to this mechanism and account for a considerable percentage of cases of undifferentiated mental deficiency.<sup>62,74</sup> The pathologic mechanism of brain damage by maternal



antibodies or their effect is not clear. The recent suggestion of Wiener and Brody,<sup>71</sup> that agglutination thrombi in cerebral vessels are the cause of brain damage, needs confirmation.

Damage to the fetus by therapeutic doses of Roentgen rays or radium is well known. It may result in microcephaly, hydrocephalus, microphthalmia and other malformations.<sup>28,42,76</sup> The need for preventing the irradiation of the fetus is obvious and well recognized. Murphy<sup>49</sup> has suggested that each therapeutic irradiation of the pelvic region of a woman in the child-bearing age should be preceded by a diagnostic curettage, in order to avoid irradiating an undetected fetus. Diagnostic doses as used for roentgenograms are not known to be harmful; fluoroscopy should be done with greatest caution.

It should be clear that this well-established cause of malformations is different from the more problematic effect of radiations on the genotype, producing mutations which determine hereditary malformations in the offspring. The occurrence of the latter process, and causation of malformations by it in man has not been established,<sup>37</sup> yet, most authors advise protection of the gonads from irradiation, unless their generative activity is completely destroyed.<sup>48,50,53,58</sup>

Malformations of unknown cause and origin cannot be prevented. Here our efforts must be directed toward the recog-

nition of the causes or, in some suitable cases, toward correction of the defect before it produces mental deficiency. The latter has been done with good success in certain cases of hydrocephalus.<sup>46,56</sup>

Birth injury by anoxia has already been discussed. Mechanical injury of the brain or meninges, usually accompanied by hemorrhage, has occupied the mind of obstetricians to a great extent, and should be rare under proper obstetrical care. In recent years the surgical removal of subdural hematomas has contributed to the prevention of cerebral and mental changes when injury had occurred.<sup>37</sup> The obstetrician's difficulties are increased by the fact that procedures which diminish the duration of anoxia during labor, tend to increase the danger of mechanical trauma, and *vice versa*.

**Conclusion.** This brief review shows that there is hardly one field in medicine which cannot contribute information needed for the prevention of mental deficiency, blindness and deaf-mutism. Just how many cases are due to each of the above-mentioned factors may not be known until they can be prevented. In view of the information now at our command, we can no longer say that antenatal causes of mental deficiency are beyond our control. The cost of the most extravagant research program in this field may well turn out to be lower than the savings of our communities resulting from a reduced number of inmates in their institutions.

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## STUDIES ON EXPERIMENTAL PHOSGENE POISONING\*

## IV. THE EFFECT OF "PRESSURE BREATHING" ON THE PULMONARY EDEMA OF PHOSGENE POISONING

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THE procedure of artificially raising intratracheal pressure, which is herein referred to as "pressure breathing," was first applied in the treatment of pulmonary edema by Emerson in 1909.<sup>10</sup> It successfully tided animals over the acute edema produced by a large dose of epinephrine. A number of years later it was employed clinically by Barach in the treatment of bronchial asthma, pulmonary edema of various origins, and other forms of respiratory distress with apparently good results.<sup>1,2</sup> Trial of this procedure in the treatment of the pulmonary lesions produced by phosgene and other lung irritants was suggested because many of the signs and symptoms of such war gas poisoning present an analogy with bronchial asthma, in addition to the massive pulmonary edema.<sup>8</sup>

Pressure breathing has been regarded as a valuable therapeutic aid when it was applied in cases of lung damage produced by chlorine and other pulmonary irritants.<sup>6,13</sup> A similarly favorable evaluation has been made in cases of accidental phosgene poisoning.<sup>14a</sup> It is not certain, how-

ever, that pressure breathing was the most important of the several therapeutic procedures employed and up to the present it has not been demonstrated that pressure breathing is of critical value in the treatment of poisoning by lung irritants. The value of pressure breathing in the treatment of the victims of the Coconut Grove fire is similarly uncertain.<sup>4,9,11,16</sup>

The experiments described below were designed to determine whether pressure breathing increased the ultimate survival rate of phosgene-poisoned dogs. Two forms of pressure breathing were employed: (1) pressure on expiration only, and (2) pressure on inspiration with a slight resistance at the onset of the expiratory phase. The results obtained with these 2 procedures did not warrant trial of maintaining a constant positive pressure throughout the respiratory cycle.

**Methods.** The dogs used in these experiments were healthy adult mongrels, weighing 7 to 12 kg. They were gassed in pairs or fours by the 2 methods previously described,<sup>6</sup> the high concentration-short duration and

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the low concentration-long duration exposures. Within the ranges indicated in these experiments, concentration and time may be varied reciprocally by a factor of 10 without significantly affecting mortality or physiologic or pathologic findings. One dog of each pair became a simultaneous toxicity control by lottery.

Immediately after gassing the treated animal was lightly restrained on its side on a table and pressure breathing with oxygen for 50 minutes of every hour was administered for the first 36 hours after gassing, or until death within that time. This regimen was designed to obviate any possibility of oxygen poisoning and yet be sufficiently protracted to carry the animal over the period in which the vast majority of deaths occur. In the interval the dog was offered food and water and turned to the other side. Each treated animal was under the continuous individual supervision of an attendant.\* The control animals were placed in nearby individual cages with food and water and were undisturbed except for the routine observations on heart rate, respiratory rate and hematocrit values which were made at regular intervals on the dogs of both groups. Animals which died were either autopsied at once, or stored at  $-4^{\circ}\text{C}$ . overnight. Survivors of the 36 hour treatment were placed in cages beside the control dogs and kept under observation for 5 days. Subsequently survivors were cared for in the regular animal quarters.

Pressure breathing on expiration was administered by means of a close fitting metal mask equipped with valves which permitted inspiration at atmospheric pressure from a reservoir bag, and directed the expiration against a hydrostatic pressure head of 6 cm.  $\text{H}_2\text{O}$ . The dead space of the mask and tubing between the valves was 100 to 200 cc., depending on the size and shape of the dog's muscle. The tubing and valves were those used in the  $\frac{7}{8}$  inch diameter air lines for human experiments; there was no intrinsic resistance to air flow in the apparatus.

Pressure breathing on inspiration was administered by means of a device† on the metal mask which consisted essentially of a

reciprocating valve linked to a demand-valve diaphragm and a source of compressed gas; the reciprocal valve mechanism was actuated by the animal's own breathing movements. The valves were set so that when the dog developed  $-0.3$  cm.  $\text{H}_2\text{O}$  pressure at the onset of inspiration, the inflow valve on a 3 pound pressure line opened and the expiratory valve closed; when the pressure inside the mask (and the animal's trachea) had built up to  $+6$  cm.  $\text{H}_2\text{O}$  pressure, the inflow valve closed and the expiratory valve opened, permitting almost resistance-less expiration. A hand adjustment controlled the volume rate of gas inflow so as to build up a positive pressure within the time allotted to inspiration by the dog without creating a blast effect. It was possible to keep this type of pressure breathing on an animal breathing as rapidly as 100 per minute.

**RESULTS.** *Pressure Breathing on Expiration.* The data on this form of pressure breathing are grouped according to the type of exposure to phosgene (CG) and whether oxygen or air was breathed by the dogs. These data are assembled in the upper 4 brackets of Table 1, labelled A, B, C and D.

Group A: These dogs were gassed for 30 minutes at a mean concentration of 0.293 mg./liter. The treated dogs then received pressure breathing on expiration (6 cm.  $\text{H}_2\text{O}$ ) for 50 minutes of every hour for 36 hours, using 100% oxygen as the inhaled gas. A beneficial effect on mortality was not observed, nor was the pulmonary edema decreased by the treatment, according to the lung/body weight ratios of those that died within 72 hours.

Group B: These dogs were gassed at a mean concentration of 3.19 mg./liter for  $2\frac{1}{2}$  minutes, and given pressure breathing as in Group A. The series was terminated when the low control mortality became apparent. While the number of dogs is too small for evaluation, the results are in line with those of Groups A and C, and are taken to indicate that use of lower

\* We wish to express our appreciation of the coöperation and courtesy of Capt. Jesse W. Allen and Capt. Joseph A. Biello, USN, through whom the services of a group of Medical Corpsmen were obtained.

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mortality rates would be unlikely to affect the general interpretations.

Group C: The dogs in this group were gassed at a mean of 3.24 mg./liter for  $3\frac{1}{2}$  minutes and received pressure breathing on expiration, using 100% oxygen, as in Group A, except that the mask was removed for 5 minutes of every  $\frac{1}{2}$  hour. No evidence of benefit was observed, as judged by either the mortality or the lung/body weight ratios.

tance. This group is also a control for Group C, insofar as increased oxygen need due to the work of exhalation against a resistance is concerned. Here, too, no evidence of real benefit was observed.

The data of these 5 groups of experiments uniformly deny the possibility that pressure breathing increases survival in experimental phosgene poisoning, despite the additional use of oxygen under conditions which should preclude oxygen poison-

TABLE 1.—THE EFFECTS OF PRESSURE BREATHING ON THE MORTALITY OF PHOSGENE-POISONED DOGS

(Groups A, B, C and D received pressure breathing on expiration, while Group E received pressure breathing on inspiration, for the first 36 hours after gassing. See text for details of procedures and doses of phosgene.)

Procedure	No. dogs	Cumulative deaths at:						In dogs dying within 3 days			
								Hours of survival		Lung/body weight	
		12 hrs.	24 hrs.	36 hrs.	48 hrs.	3 days	10 days	Mean	Range	Mean	Range
A Treated	23	4	10	12	15	16 (70%)	19 (83%)	22.6	(1.6-52.5)	4.6	(2.5-6.4)
	Control	23	6	11	12	13	14 (61%)	21.1	(8.0-72.0)	4.6	(3.4-5.8)
B Treated	5	1	2	2	3	3 (60%)	3 (60%)	19.5	(4.0-36.5)	3.2	(2.0-4.0)
	Control	5	0	0	0	1 (20%)	1 (20%)	36.5		4.1	
C Treated	10	3	6	7	9	9 (90%)	9 (90%)	20.5	(9.0-45.0)	4.2	(3.1-4.9)
	Control	10	6	6	6	6 (60%)	6 (60%)	8.2	(6.0-10.5)	4.2	(2.8-5.3)
D Treated	16	10	16	16	16	16 (100%)	16 (100%)	12.8	(4.0-20.8)	3.8	(3.0-4.8)
	Control	16	3	9	12	12 (75%)	12 (75%)	17.0	(8.0-32.0)	4.3	(3.2-5.3)
E Treated	22	9	13	13	16	17 (77%)	19 (86%)	21.6	(7.0-50.0)	4.2	(2.9-6.1)
	Control	24	3	13	18	19 (79%)	19 (79%)	18.1	(4.0-46.0)	4.2	(3.2-6.7)

Group D: These dogs were gassed with the same doses of phosgene as Group C, but inhaled air instead of oxygen. This group was designed as a control on the procedure and the use of oxygen in connection with pressure breathing. It appears that the oxygen was responsible for whatever prolongation of life occurred in the other groups. Both the disproportionate number of early deaths and the decreased ultimate survival in this group are evidence that the procedure was valueless, if not actually harmful.

Group E: *Pressure Breathing on Inspiration.* These dogs were exposed to a mean phosgene concentration of 3.29 mg./liter for  $3\frac{1}{2}$  minutes and then were given pressure breathing on inspiration during 50 minutes of each hour for 36 hours; the inspired gas was 100% oxygen. As indicated above, inspiration was made almost completely passive by the mechanism and expiration was essentially without resis-

ing. Two changes were observed under pressure breathing which are desirable symptomatically: (a) the respiratory rate was generally slower during either type of pressure breathing with oxygen; (b) application of pressure breathing when râles were present caused the râles to disappear almost completely except shortly before death. On the other hand, the râles promptly returned when pressure breathing was discontinued. Also the rate of development of edema under pressure breathing was comparable with that of the controls according to the hematocrit changes, and the final degree of edema in the lungs at death was similar in the control and treated groups, as judged by the lung/body weight ratios. The changes in heart rates of control and treated animals were similar throughout.

In another series of 9 gassed dogs (not included in the table) pressure breathing on expiration at 4 to  $6\frac{1}{2}$  cm.  $\frac{1}{2}$  H<sub>2</sub>O pressure

with oxygen was applied for 2 to 3 hours at various periods in the course of poisoning in different dogs. Again, no reduction in mortality was observed.

**Discussion.** These experimental data fail to bear out the expectations warranted by the previously cited clinical evaluations. Therefore it is of interest to examine the mechanism by which pressure breathing might influence the course of phosgene poisoning. It should be recalled that the edema fluid of phosgene poisoning is essentially blood plasma and that it forms as a result of an increased capillary permeability and not because of a raised pulmonary vascular pressure gradient.<sup>8,12</sup>

Pressure breathing has been conceived to exert in effect a net positive tissue pressure which complements the colloidal osmotic pressure in keeping fluid within the vessels. This conception implies a more or less normal capillary permeability and therefore it is unlikely that such a mechanism would be effective in phosgene poisoning. Conversely, pressure breathing might promote the formation of edema. If the applied pressure is less than pulmonary capillary pressure, the small veins and postcapillary venules would be compressed more effectively than the rest of the vasculature and the flow through them would be reduced or even stopped. This would cause a "backing up" of hydrostatic pressure in the capillaries with establishment of a new pressure gradient.<sup>7</sup> It is not clear whether the net effect on the capillaries would always come to zero,<sup>15,17</sup> as an attempted numerical analysis failed because of inadequate knowledge of the pressure gradients in such a lung. The principle of venous obstruction, however, is demonstrable in the case of experimentally raised cerebrospinal pressure and it should apply here too.

A part of the positive pressure is transmitted through the pleura and applied to structures entering the thorax with the result that the entrance of blood into the thorax is hindered.<sup>1,5,7,14,15,17</sup> Although the positive pressures employed in those

experiments were usually higher than that used in the present work, some reduction of flow through the lungs is to be anticipated, as well as a squeezing forward of blood which is more or less static in the lungs. On the one hand, this might be beneficial in reducing the pulmonary congestion seen in phosgene poisoning,<sup>8</sup> but on the other hand it may accentuate the shocklike hemodynamics and exaggerate the anoxemia. Beecher *et al.*<sup>5</sup> and Carr and Essex<sup>7</sup> have observed that the circulatory effects of pressure breathing were magnified when the animal's circulation was poor. From this standpoint the net effect of pressure breathing is probably deleterious, although it still remains problematical.

Another effect of pressure breathing is dilatation of the bronchi and bronchioles; this has been demonstrated roentgenographically.<sup>3,7</sup> During the acute stage of phosgene edema, the viscous edema fluid enters the bronchioles and eventually forms a froth which acting as a "water-lock" stops the gas exchange. Pressure breathing should facilitate the passage of air or oxygen to the alveolar regions by widening available routes and by breaking through these "water locks." It is reasonable to ascribe the prompt disappearance of râles to this dilator action of pressure breathing; reduction or disappearance of râles, however, is not necessarily evidence of resorption of edema fluid.

The experiments reported here may be criticized on the basis that the pressure employed for pressure breathing (6 cm. H<sub>2</sub>O) was too low to be really effective. However, in preliminary experiments, this pressure was found to be the maximum which was tolerated by the dogs for any extended periods. Furthermore, this is the highest pressure with which favorable clinical results were obtained.

Pressure breathing on expiration was apparently associated with considerable effort; the extra oxygen need created by such work probably was in part responsible for the increased mortality in Group D. This added effort was not apparent with

pressure breathing on inspiration, which in addition almost completely removes negative pressure in the lungs during the respiratory cycle. Of the 3 systems of administration, pressure breathing on expiration seems to be the least desirable, although it is the most convenient.

These results indicate that pressure breathing would be ineffective or even harmful in phosgene poisoning in man. Apparently pressure breathing is either not suited, or is not sufficiently comprehensive to deal with the anatomic and functional damage found in phosgene poisoning.

**Summary.** 1. Pressure breathing with oxygen at 6 cm.  $H_2O$ , both on inspiration and on expiration, was administered to phosgene-poisoned dogs for the first 36 hours after gassing. No reduction in mortality was observed and according to the hematocrit changes and the lung/body weight ratios at death, neither the rate of development nor the final degree of pulmonary edema was influenced by such treatment.

2. Certain of the data suggest that such treatment may be harmful in phosgene poisoning and the effects of pressure breathing on the circulation are discussed from that point of view.

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## THE ANATOMY OF THE PANCREATIC DUCTS

## THE ETIOLOGY OF ACUTE PANCREATITIS

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THE anatomy of the pancreatic duct system and of its relationship to the lower end of the common bile duct has been a subject of much interest since 1901 when Opie<sup>25</sup> first presented his "common channel" theory of the etiology of acute hemorrhagic pancreatitis. This theory found its origin in Opie's now classic autopsy study of a case of acute hemorrhagic pancreatitis in which he found a small biliary calculus impacted in the papilla of Vater, converting the duct of Wirsung and the common bile duct into a common channel so that there had been a reflux of bile into the main pancreatic duct. The theory that the pancreatitis had been caused by the reflux of bile into the pancreatic tree was well founded because Claude Bernard<sup>6</sup> had previously shown that the injection of a mixture of bile and olive oil into the pancreatic duct produced the disease in experimental animals. That acute, hemorrhagic pancreatitis can be produced by such an injection of bile has been shown by numerous investigators.<sup>1,2,3,11,12,13,22,24,25,27,37</sup> Opie's theory has subsequently been the subject of much study and considerable criticism; but many authors<sup>20,35,36</sup> now agree with Dragstedt's<sup>10</sup> opinion that the common channel theory probably explains 60 to 70 % of cases of the disease that occur in man.

It was originally thought that a calculus impacted at the ampulla of Vater was responsible for the formation of a common channel in all cases of pancreatitis,<sup>25</sup> but subsequent autopsy studies have shown that a calculus is the obstructing agent in not more than 10 % of clinical cases of this disease.<sup>10</sup> On the basis of Archibald's<sup>1</sup>

work in animals it is now believed that segmental spasm of the sphincter of Oddi is the obstructing agent which creates the common channel in most clinical cases of the disease.

There are 2 important prerequisites that must be fulfilled before Opie's common channel theory can be accepted. The first of these, as Opie realized,<sup>24</sup> is that the anatomic possibility for the formation of a common channel in a reasonable percentage of people must be established. It is obvious that the 2 ducts must unite to form a common ampulla before emptying into the duodenum and that the union must occur at a sufficient distance from the duodenal orifice to allow for obstruction of the orifice without obstruction of either of the ducts.

That a common channel exists in a limited number of persons has been proved *in vivo* by cholangiography. This study does not necessarily demonstrate all cases in which reflux is possible, but it does offer evidence *in vivo* that reflux is anatomically possible. Table 1 indicates the results of such studies by several investigators.

TABLE 1.—DEMONSTRATION OF THE PANCREATIC DUCT IN CHOLANGIOGRAPHIC STUDIES (IN VIVO STUDIES OF THE REFLUX OF FLUID FROM THE COMMON BILE DUCT INTO THE MAJOR PANCREATIC DUCT)

Author	No. patients	Incidence of reflux	
		No.	%
Colp and Doubilet <sup>3</sup>	35	7	20
Robins and Hermanson <sup>29</sup>	25	4	16
Hunt, Hickson, Best <sup>15</sup>	56	5	9
Leven <sup>19</sup>	91	21	23
Mirizzi <sup>23</sup>	800	"frequent"	



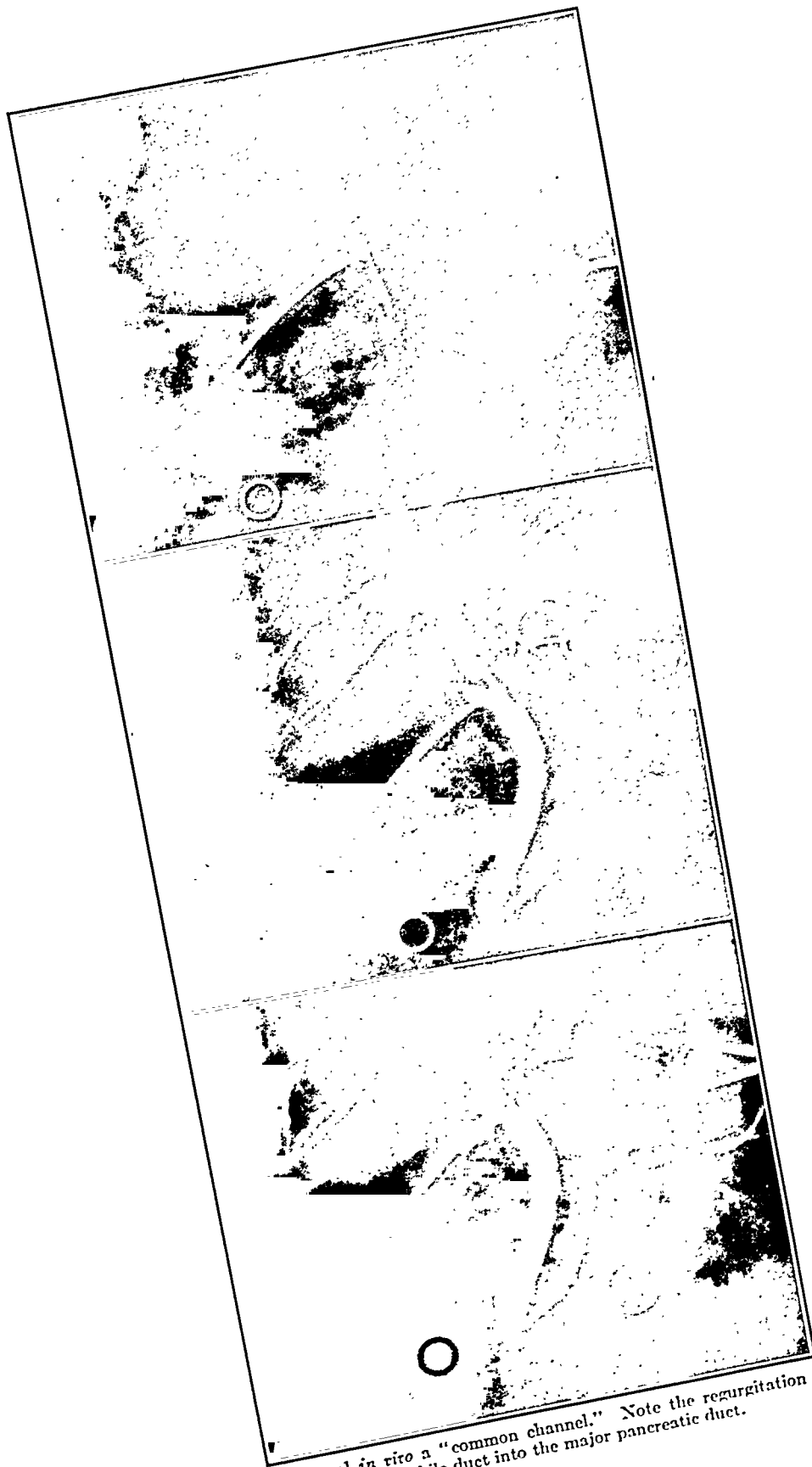


FIG. 1 -Serial films reveal *in vivo* a "common channel." Note the regurgitation of fluid from the common bile duct into the major pancreatic duct.

The second important prerequisite is that once a common channel is formed the direction of flow in that channel must be in the direction of the pancreas rather than the reverse. It would seem that the direction of flow in such a system would depend upon the relative pressures existing in the 2 ducts. This has been considered, and it has been shown that in animals the maximal secretory pressure of the pancreas equals or exceeds that of the liver.<sup>10,21</sup> This has been considered strong

investigated by numerous workers in the last 40 years, but the results have been amazingly divergent. Table 3 summarizes the results of previous studies of the problem.

TABLE 2.—INCIDENCE OF PATENT DUCT OF SANTORINI CONNECTING DUCT OF WIRSUNG WITH DUODENUM

Author	No. cases	Patent at both ends
Opie <sup>24</sup>	100	52
Simpkins <sup>24</sup>	25	12
Rienhoff-Pickrell <sup>28</sup>	100	62
Present series	150	36

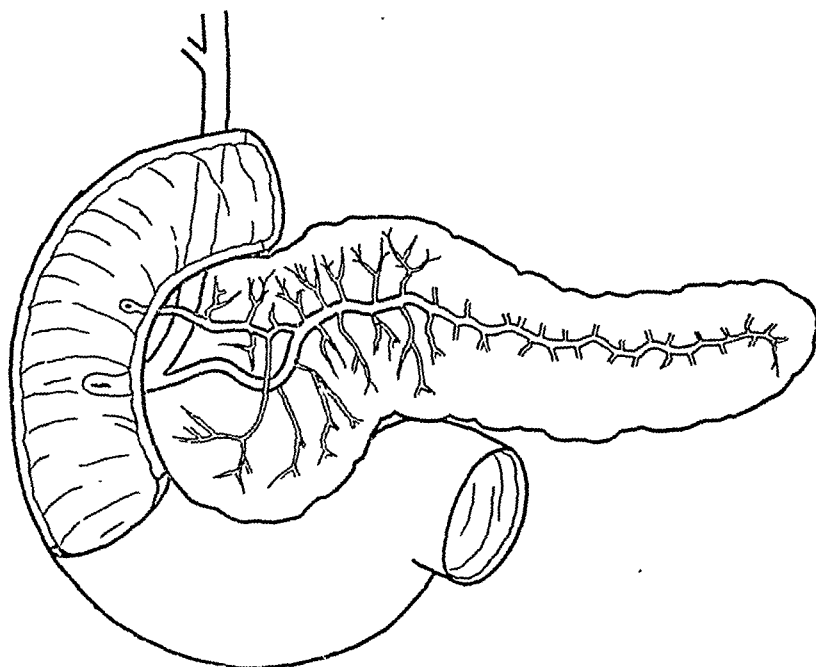


FIG. 2.—The pancreatic ducts. The ampulla of Vater is illustrated at the junction of the major pancreatic duct with the common bile duct.

evidence against the common channel theory because the onset of acute hemorrhagic pancreatitis usually occurs about 2 hours after a heavy meal when the secretory activity of the pancreas is maximal.<sup>10</sup> Dragstedt, Haymond and Ellis<sup>10</sup> feel that the secretory pressures are not the only factors determining the direction of flow. They have stated that if a patent duct of Santorini connects the duct of Wirsung with the duodenum, the secretory pressure of the pancreas would be nullified because the duodenal orifice of the duct of Santorini has no sphincter (Table 2, Fig. 2).

The anatomy of the ampulla of Vater and the relationship of the bile and pancreatic ducts at this point have been

Opie,<sup>24</sup> in 1901, dissected this region in 100 fixed specimens and found that in 89 the ducts united to form a common ampulla, and in 11 they opened separately into the duodenum. He concluded that the ampulla must be 5 mm. or more in length if an impacted stone is to cause reflux into the duct of Wirsung. He found that on this basis the anatomic possibility for the formation of a common channel existed in 30% of his specimens. Mann and Giordano<sup>21</sup> studied fixed specimens from 200 consecutive autopsies by dissection. They found that both ducts opened separately in 31% of cases and that in 45% of cases the ampulla was less than 2 mm. in length. They found the am-

pulla to be 5 mm. or more in only 3.5% of cases and felt that in only these cases could a common channel possibly be created. This study was felt by many to have cast serious doubt on the common channel theory. Many other studies (Table 3) on fixed specimens have given similar results.

embryologic development of the ampulla of Vater in 18 human embryos and fetuses and came to the following conclusion: "The ampulla . . . is at first coextensive with the oblique intramural passage of the duodenum, but beginning at the 30 mm. stage the point of junction of the bile and pancreatic ducts recedes from

TABLE 3.—STUDIES ON THE INCIDENCE AND SIZE OF THE AMPULLA OF VATER

*Fixed Specimens—Dissection Method*

Author	Date	No. specimens	Ampulla present	No ampulla	Ampulla over 5 mm. length	Reflux possible
Schirmer <sup>21</sup>	1893	48	25	23		
Letulle and Nattan <sup>18</sup>	1898	21	8	15		
Opie <sup>25</sup>	1903	100	89	11	30.0	30.0
Ruge <sup>30</sup>	1908	43	32	11		
Osler <sup>26</sup>	1908	100	..	..	..	32.0
Baldwin <sup>4</sup>	1911	90	70	20		
Belou <sup>5</sup>	1915	50	23	27		
Judd <sup>17</sup>	1921	170	..	..		4.5
Mann and Giordano <sup>21</sup>	1923	200	130	70	3.5	3.5
Job <sup>16</sup>	1926	116	..	..	5.3	
Schmieden and Sebening <sup>22</sup>	1927	35	..	..	..	32.0
Hozapfel <sup>14</sup>	1930	50	10	40		
Dardinski <sup>9</sup>	1936	100	49	51	8.0	
Rienhoff-Pickrell <sup>*23</sup>	1945	250	81	169	19.0	32.0

*Unfixed Specimens—Injection Method*

Cameron and Noble <sup>7</sup>	1924	100	74	26	48.0	66.0
Present series	1946	150	109	41	26.0	54.0

\* 100 fresh specimens included.

In 1924 Cameron and Noble<sup>7</sup> investigated the anatomy of this region with reference to the common channel theory in fresh specimens, using a more physiologic method. They placed a small, roughly spherical gall stone in the common bile duct and manually stripped it downward until it became impacted at the ampulla. They then injected fluid into the common bile duct under a pressure of 100 mm. of water and found that reflux into the pancreatic duct occurred in 66% of 100 specimens. Subsequent dissection revealed that the average length of the ampulla in these specimens was 6.7 mm. They found that a true ampulla was formed in 74% of 100 specimens. This work was accepted by Dragstedt, Haymond and Ellis,<sup>19</sup> and others as having conclusively settled the question of the anatomic basis for the common channel theory.

Schwegler and Boyden<sup>23</sup> studied the

the window in the intestinal wall into the submucosa until, near term, it lies half way between the tunica muscularis and the end of the papilla."

On the basis of this work and supported by the studies of Job,<sup>16</sup> Dardinski,<sup>9</sup> Mann and Giordano,<sup>21</sup> and others (Table 3), they stated that "pancreatitis resulting from regurgitation of bile into the *ductus pancreaticus* is theoretically possible in a very small per cent of individuals." They criticized the work of Cameron and Noble,<sup>7</sup> implying that their results may well have been due to an artefact produced by rupture of the membranes separating the distal ends of the 2 ducts when the gall stone was stripped down to the ampulla.

**Methods.** This study consisted of examination of 150 fresh, unfixed specimens consisting of pancreas, duodenum and common bile duct removed intact at autopsy at the Philadelphia General Hospital. Our method was as follows: The common bile duct was

dissected free to the duodenal wall. The major pancreatic duct was picked up close to its junction with the common bile duct and exposed for a sufficient distance to insure adequate visualization. In 102 specimens the method of Cameron and Noble<sup>7</sup> was followed, that is, a small calculus was manually stripped down the common bile duct until it became impacted into the ampulla. Colored fluid was then injected into the common bile duct under a pressure of 500 mm. of water instead of 100 mm. as was used by these investigators. In 48 specimens the duodenum was opened and the papilla of Vater was occluded by clamping it with a small mosquito hemostat. A cannula was tied into the common bile duct, and a colored fluid was injected into it under low pressure by means of a syringe. If reflux of the fluid into the duct of Wirsung occurred, the duct was distended, and the fluid could be seen escaping from pin-point holes in the wall produced when the duct was dissected free from adjacent parenchyma.

In each of the 150 specimens the major duct was then clamped off close to its junction with the common bile duct, and fluid was injected into it through a cannula in the tail of the gland in order to determine the number of cases in which a patent duct of Santorini connected the duct of Wirsung with the duodenum. At the end of the experiments the duct of Wirsung and the common bile duct were carefully opened to the tip of the papilla with a pair of fine scissors. The septum between the 2 ducts was carefully examined in all cases for evidence of tearing or perforation, and the depth of the ampulla was measured.

**RESULTS.** 1. In 81 of 150 cases (54%), a common channel was created by the methods described, and reflux of the injection fluid into the duct of Wirsung occurred. In 69 (46%) no reflux was demonstrated.

2. A patent duct of Santorini connecting the duct of Wirsung with the duodenum was demonstrated in 36% of 150 cases. A comparison with results of previous studies in which this was considered is shown in Table 2. In 44% of the 81 cases in which reflux at the ampulla of Vater occurred, a patent duct of San-

torini connecting the duct of Wirsung with the duodenum was demonstrated.

3. The results of measurement of the ampulla are shown in Table 3. Reflux occurred in 2 cases in which the ampulla was 2 mm. and in all cases in which it was 3 mm. or more in length.

4. In no case was any evidence of tearing or perforation of the septum between the 2 ducts detected.

This study confirms the findings of Cameron and Noble,<sup>7</sup> and there was no evidence on macroscopic examination that the membrane between the 2 ducts at the ampulla had been torn or perforated. The pressure selected was approximately that which was found to be the minimal pressure necessary *in vivo*<sup>21</sup> for injection into the pancreatic duct of dogs. The injection method, using fresh material, is a more physiologic approach to the problem of the incidence of an anatomic arrangement which makes it theoretically possible to create a common channel, connecting the pancreatic and common bile ducts at the ampulla of Vater, than is simple dissection with measurement of the ampulla. It is, therefore, believed that Cameron and Noble's<sup>7</sup> conclusion is valid, that in at least one-half of all persons the possibility of the formation of a common channel exists. It should be pointed out that in all of the studies which would indicate that this is not the case the specimens examined have been preserved in some fixative solution. These substances all cause some shrinkage of tissue, and this factor could certainly alter the measurement of the depth of the ampulla from that which was present in the fresh specimen. Moreover, when measurement of the ampulla is the only criterion by which the possibility of the occurrence of reflux is determined, the factor of the elasticity and distensibility of the walls of the ampulla cannot be estimated. This must certainly play a part in determining whether or not reflux occurs when the obstructed papilla is subject to the pressure of bile that exists in the common duct. For these reasons it is prob-

able that the results of studies in which fixed tissue is used do not represent the conditions that exist in the living body.

It is of possible significance that the group of specimens in which reflux from the common bile duct to the duct of Wirsung constituted only 54% of the total group studied but contained 82% of the specimens in which the duct of Santorini was patent from the duct of Wirsung to the duodenum.

**Summary.** 1. When the papilla of Vater was obstructed by a small calculus or was clamped by a hemostat, fluid injected into the common bile duct regurgitated into the duct of Wirsung in 81 (54%) of 150 fresh specimens.

2. The duct of Santorini was shown to be patent from the duct of Wirsung to the duodenum in 54 (36%) of 150 specimens. This occurred in 44 of the 81 cases in which a reflux was demonstrated and in only 10 of the 79 cases in which no reflux occurred.

3. The common duct and the main pancreatic duct united to form an ampulla in 109 cases. In 41 cases the 2 ducts opened separately into the duodenum.

**Conclusions.** Evidence is presented which confirms the finding of Cameron and Noble<sup>7</sup> that the anatomic possibility for the formation of a common channel at the ampulla of Vater exists in at least 50% of persons.

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## THE CORONARY ARTERIES OF INFANTS\*

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CONSIDERING the enormous volume of literature devoted to the coronary arteries, the dearth of attention given these vessels in newborns, infants and children is rather surprising. A few investigators have included the coronary arteries of young people in overall surveys of age changes occurring in these vessels; none of these has studied infantile coronary arteries in numbers adequate for statistical analysis. To meet this need, there are here reported the histologic studies on the coronary arteries of 204 infants, most of whom died at or soon after birth.

Jores,<sup>7,8</sup> Bork,<sup>2</sup> and Wolkoff<sup>19,20</sup> explored arterial changes with age. They described a pattern of intimal development in very small numbers of newborns and children which has been accorded widespread acceptance. In brief, they noted that the first departure from the normal coronary intima (which may be defined as a single layer of endothelium covering the intact internal elastic lamella) is a splitting of the internal elastic lamella to form the internal limiting lamella; when medial muscle cells migrate through the internal elastic lamella into the space between these elastic laminae, the musculo-elastic layer is formed. The elastic hyperplastic layer arises from the internal limiting lamella by splitting off from the latter. It is this layer which may assume primary significance in the development of atherosclerosis, for in it collagen, lipoid and calcium may be deposited. Ehrlich, de la Chapelle, and Cohn<sup>4</sup> observed the musculo-elastic layer at the origin of the anterior descending artery in the hearts of all 5 of their newborns (4 males and 1 female) and in the right coronary artery in 1 newborn. None of the coronary arteries of

their newborns revealed an elastic hyperplastic layer. Both the musculo-elastic and elastic hyperplastic layers were found with increasing frequency in the 2nd decade, but in this age group, too, the number of hearts examined was very small.

In 1934 Gross, Epstein and Kugel<sup>5</sup> reported on the histology of the coronary arteries with particular emphasis on the changes occurring with age in each of the major rami. They studied a total of 50 hearts selected in such a way as to eliminate diseases which might affect the coronary arteries; however, they did not include the diagnoses nor did they indicate the number of hearts in any age group. Their observations may be summarized briefly: The musculo-elastic and elastic hyperplastic layers were found at birth in the left anterior descending artery, in the left circumflex artery between the 3rd and 12th month, and in the right coronary artery at about the 12th month. These findings are not in close agreement with those of Ehrlich, de la Chapelle and Cohn just cited. Moreover, none of the aforementioned authors<sup>2,4,5,7,8,19,20</sup> either directly or by implication suggested any sex difference in the time of appearance or degree of development of these intimal changes.

The significance of these intimal changes, particularly with respect to the future development of atherosclerosis is not entirely clear. Concerning splitting of the internal elastic lamella and the formation of a musculo-elastic layer, there is no unanimity of opinion. It is claimed that these changes are physiologic, a view presumably supported by the fact that they occur during the period of active arterial growth, and because, according to Bell,<sup>1</sup>

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there are rarely any retrogressive changes in the intima during this period. On the other hand, Jores<sup>7</sup> considered any splitting of the elastic lamina a manifestation of arteriosclerosis. McMeans<sup>12</sup> demonstrated that any inflammatory or toxic substance acting in sufficient concentration results in a dissolution or alteration in this elastic lamina and gives the appearance of splitting. He felt that any splitting or alteration of this sort, once induced, is permanent and may be increased by further injury. Moreover, MacLean's<sup>10</sup> support of the notion that any alteration in the internal elastic lamella and overlying endothelium is pathologic rests on the commonplace observation that these changes, even in mild form, may be absent in the coronary arteries of elderly individuals, while very striking in those of children and young adults.

Essential unanimity exists with regard to the significance of the elastic hyperplastic layer. Jores<sup>7,8</sup> contended that this layer is pathologic, pointing out that it occurs without uniformity from vessel to vessel and within the same vessel, and that he noted transitions from the elastic hyperplastic layer to processes unequivocally pathologic. Jores believed this layer to represent a compensatory response to increased intravascular pressure. Ehrlich, de la Chapelle and Cohn<sup>4</sup> stated that the elastic hyperplastic layer may serve as the anlage for the development of atherosclerosis by virtue of its thickness which predisposes it to nutritional disturbances. Gross, Epstein and Kugel<sup>5</sup> were convinced that gradations from the elastic hyperplastic layer to atherosclerosis could readily be seen in their material.

In 1946 Dock<sup>3</sup> wrote a unique and stimulating paper on the coronary arteries in the newborn in which he approached the subject from the point of view of establishing a sex difference in thickness of the newborn coronary intima. Employing 12 males and 12 females less than 1 day old, he cut cross-sections from each of the major coronary rami, stained them by

the Weigert-van Gieson method, drew the intima and media at a magnification of 100 diameters, and calculated their surface areas. The intima-media ratio was used as the variable, and analysis of his data enabled him to state that the newborn male coronary intima is about 3 times as thick as that of the newborn female. From this he concluded that: "This is believed to establish the basis for the sex difference in the incidence of coronary occlusion and to prove that the predilection of atherosclerosis for the coronary arteries is due to their possessing an intima varying in thickness from 10 to 600% of that of the media and averaging 26% in newborn males and 8% in females."

**Method and Material.** Tables 1 and 2 list the age groupings and diagnoses of our material, including 122 males and 82 females. The vast majority were stillborns and newborns less than 1 week old. The causes of death were, in general, limited to birth injuries and/or asphyxia, inflammatory processes, and a small number of miscellaneous diseases unrelated to either of the former groups. Sections about 5 mm. thick were taken from each of the 3 major coronary arteries at 0.5 to 1 cm. from their origins. A small transverse section was also taken from the base of the aorta. All material was fixed in formalin and embedded in paraffin. Sections 6 micra thick were routinely stained with hematoxylin and eosin. Where desirable additional sections were stained for elastic and collagenous tissue. The hematoxylin-eosin and/or elastica sections were photographed directly on enlarging paper at magnifications of 24 to 154 times. A standard hemocytometer was photographed on film at the same magnifications. The areas of intima and media were then measured directly by superimposing the transparent film with properly magnified scale on the paper negative and the ratio of intima to media was calculated. In the context of this paper the term intimal thickening refers to the musculo-elastic and/or elastic hyperplastic layers as illustrated in Figure 1 (A to D). The statistical term *sigma* refers to the probable error of the means; a difference between the means of 2 samples equal to or greater than 3 times the probable error is considered significant. A dif-

ference between 2 and 3 times the probable error is considered highly suggestive.

**Results.** From the outset the primary purpose of this study was 2-fold: to establish the existence or non-existence of a significant difference in thickness between the male and female newborn coronary

intima; and, should these data confirm Dock's report, to endeavor to shed some light upon the nature of this difference. In Table 1 the pertinent statistical data are given. In the total group of 122 males and 82 females the intima-media ratio for all 3 arteries in all age groups reveal no significant sex difference.

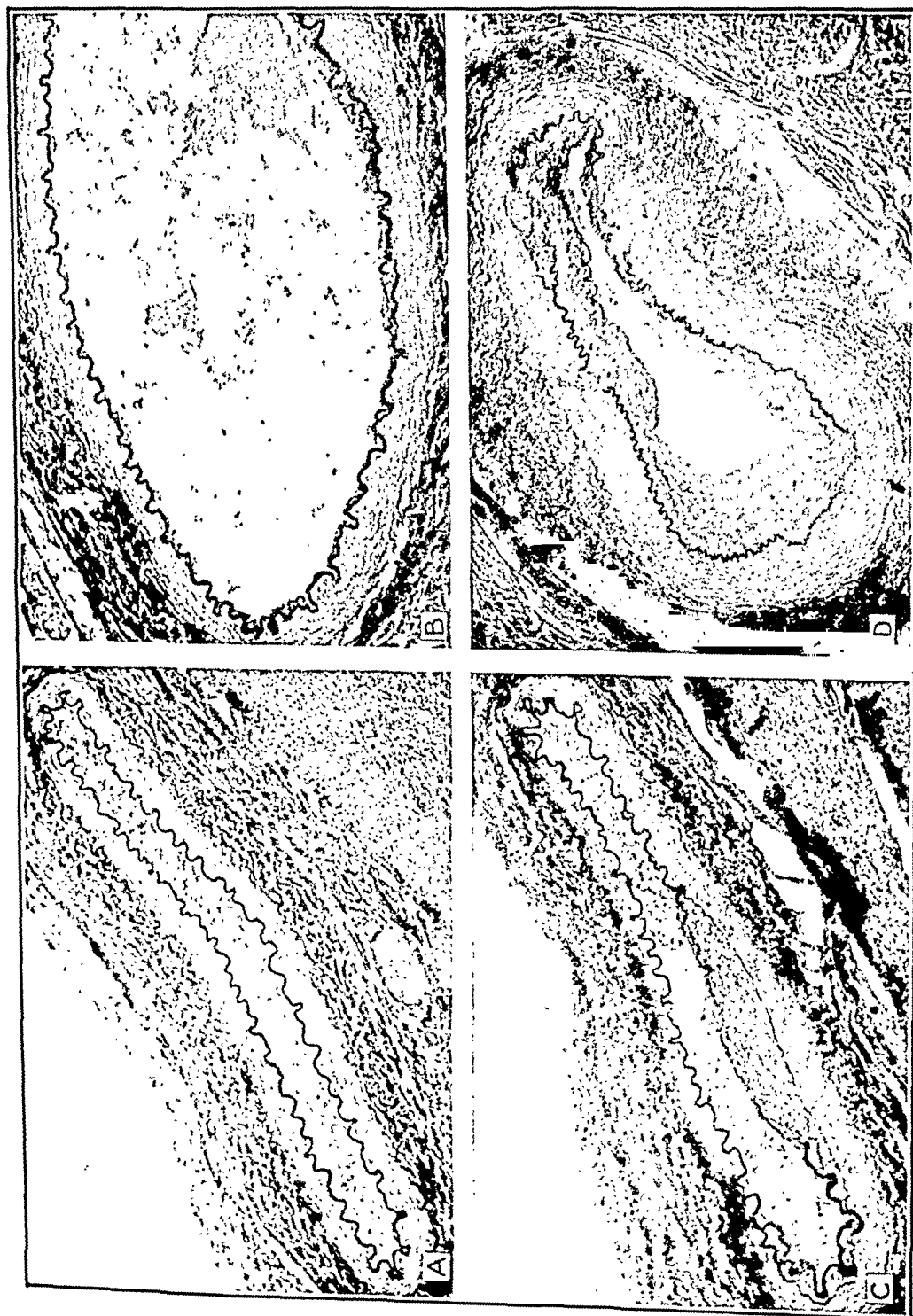


Fig. 1.—A, Coronary artery of infant with normal intima. The internal elastic lamella is intact throughout the entire circumference of the vessel. Weigert's elastica,  $\times 96$ . B, Coronary artery of infant with earliest intimal change. The internal elastic lamella shows splitting in several places. Weigert's elastica,  $\times 96$ . C, Coronary artery of infant demonstrating a well-developed elastic hyperplastic layer. Weigert's elastica,  $\times 96$ . D, Coronary artery of infant illustrating an extremely extensive elastic hyperplastic layer. Weigert's elastica,  $\times 56$ .



The total material was then subjected to age group analyses. Male:female comparisons in the following groups suggest no important sex differences: (1) all hearts up to 2 days of age (80 males, 52 females); (2) all hearts up to 1 week of age (84 males, 58 females); (3) all hearts more than 2 days of age (42 males, 30 females); and (4) all hearts up to 1 month of age (92 males, 62 females). The only group in which male:female differences are significant is the more-than-1-month-old group comprising 20 males and 20 females. The difference between the means is 5 times the probable error of the means. But in this group the validity of the difference is somewhat obscured by the fact that in the deaths of 82%

there were 51 males and 25 females. Analysis of these groups yields a highly suggestive difference between the means of 2.64 times the probable error of the means. This implies that in only 1 in 100 times chance factors might have produced this difference.

Shortly after this study was begun, it was decided to correlate intimal thickenings with the pattern of coronary artery distribution. Applying the criteria of Schlesinger,<sup>17</sup> 170 hearts were classified as right preponderant, left preponderant, or balanced. The technique for determining the epicardial course of the coronary arteries was that of gross inspection and multiple sections across the long axis of the vessels. The notion that these intimal

TABLE 1.—AGE GROUPS AND PERTINENT STATISTICAL DATA FOR TOTAL MATERIAL

Age groups	Total	Male	Female	Probable error of means	Difference between means
All age groups . . . . .	204	122	82	0 026	0 008
Up to 2 days . . . . .	132	80	52	0 029	0 009
Up to 1 week . . . . .	142	84	58	0 023	0 015
More than 2 days . . . . .	72	42	30	0 017	0 008
Up to 1 month . . . . .	164	102	62	0 041	0 014
More than 1 month . . . . .	40	20	20	0 022	0.111
BIH group comparable to Dock's . . . . .	76	51	25	0 0037	0 0098

TABLE 2.—DIAGNOSES FOR TOTAL MATERIAL

Diagnosis	Total	Male	Female
Birth trauma and/or asphyxia . . . . .	111	66	45
Infection . . . . .	70	43	27
Miscellaneous . . . . .	23	13	10

of these cases, male and female combined, a severe inflammatory process was either the direct cause or a major contributory factor; this was true of 90% of the males and 75% of the females. The influence of infection on arterial intima has already briefly been noted in the work of McMeans in 1915. It will be discussed again in the course of this paper.

It was then felt desirable to set up a group of males and of females comparable to those employed by Dock.<sup>2</sup> Every possible extraneous factor which might conceivably affect the coronary intima was eliminated. The groups were finally restricted to infants not more than 1 day of age whose deaths could be attributed to birth trauma and/or asphyxia. In all

bolsters represent pre-arteriosclerotic lesions has been advanced by several investigators previously cited. If this is true, then one might expect the distribution of these infantile lesions to be similar to that established for the adult coronary lesion. Schlesinger<sup>17,18</sup> and his co-workers in Boston, and Ravin and Geever<sup>16</sup> in Denver have described a pattern of behavior for coronary sclerosis with respect to its distribution in each of the major coronary arteries as well as in each of the 3 arterial distribution groups described by Schlesinger. The details of our results in this regard will be reported in another paper. Suffice it to state at this time that our data reveal remarkable similarities in the dis-

tribution of the adult and infantile coronary lesions.

**Comment.** During the course of the histologic observations, it was noted that in those cases demonstrating particularly thick coronary intimas, the diagnoses were basically similar; namely, some severe inflammatory process, most often bronchopneumonia. Dissension is rife among investigators concerning the effect of infectious diseases on arterial intima. Klotz<sup>9</sup> had postulated that hematogenously disseminated bacteriotoxins injured the arterial intima in such a way as to increase its permeability to plasma lipids, thereby laying the cornerstone for subsequent atherosclerosis. In 1915 McMeans<sup>12</sup> whose work has already been mentioned, studied the coronary arteries of small groups of children, young adults and elderly people. His young hearts were obtained from children who had died of pneumonia, scarlet fever, diphtheria, meningitis and other acute infectious diseases. He concluded that splitting of the internal elastic lamella was a toxic manifestation of infections and, furthermore, that this splitting represented a permanent alteration in the artery which would later provide the base for arteriosclerotic change. It is difficult to accept these conclusions inasmuch as he had no adequate control group of hearts obtained from young patients who had died of causes other than acute infections.

In 1921 Mönckeberg<sup>13</sup> reported on his observations in children dying of acute infectious diseases, particularly influenza. He noted that the degenerative intimal changes in their coronary arteries occurred in the same places where one finds adult coronary atherosclerosis. Ophüls<sup>14,15</sup> was an early champion of the infectious origin of arteriosclerosis, but following a detailed study of 500 autopsies, concluded that "no altogether acceptable proof, however, has been furnished of this suspected interrelationship between certain infectious diseases and the later development of arteriosclerosis or of the syndrome of cardiovascular disease." MacCallum's<sup>11</sup> analysis of his own large material prompt-

ed him to the statement that "there is but little evidence in favor of the idea that infections, whether acute or chronic, play a great part in the pathogenesis of arteriosclerosis."

In Hueper's<sup>6</sup> comprehensive reviews on arteriosclerosis the toxin theory is briefly discussed. He cites the early observations of numerous European workers among whom opinion differed widely as to the effect of infectious diseases on the arterial intima. Many felt that cushion-like cellular thickenings with hyperplasia of elastic tissue as well as lipoid deposition occur in infectious diseases such as those previously mentioned. On the other hand, a smaller but none the less imposing group of men denied this relationship. Experimentally, many workers were successful in producing hyperplastic intimal thickenings (along with medial degeneration) with a variety of bacteria and bacterial products. But here, too, observations were at variance; moreover, the experimental animal used appeared to be an important factor in determining the effect of these experimental insults.

In the present series (Table 3) acute infectious diseases appear unequivocally to have elicited intimal thickenings in the form of musculo-elastic and elastic hyperplastic layers. The total material of 122 males and 82 females was divided into 2 groups: in 126 cases death was entirely unrelated to infections and in 78 cases some acute infectious process was the immediate cause of death. The difference between the means of the intima-media ratios is 5.5 times the probable error of the means, a highly significant difference. In those infants more than 1 month of age, in which age group an infectious disease is more often than not the cause of death, there were 36 infection deaths and 8 non-infection deaths. The difference between the intima-media ratio means for these groups is more than 8 times the probable error of the means.

**Conclusions.** Three facts of practical and theoretical interest appear from these data: (1) Coronary intimal thickenings

in varying degree occur in a rather large number of newborns, infants and children of both sexes (Table 4). On the basis of very small samples several investigators have described the occurrence of the musculo-elastic and elastic hyperplastic layers in the coronary arteries of infants, assuming that their findings were characteristic of given age groups. In reality Dock is the first to have reported on more than negligible numbers.

However, it is difficult to interpret Dock's

over, at best all figures are rough approximations, since only a very small segment of each artery was examined. A technique approaching genuine accuracy would demand that each artery be studied microscopically throughout a large part of its epicardial course. In any event this study has confirmed the presence of intimal bolsters of varying size in one or more of the coronary arteries of a fairly large number of newborns and children dying of various causes.

TABLE 3.—INFECTION AND NON-INFECTION GROUPS

Age groups	Total	Infection deaths	Non-infection deaths	Probable error of means	Difference between means
Total	204	70	134	0.028	0.125
More than 1 month	40	32	8	0.019	0.163

TABLE 4.—PERCENTAGE OF MALES AND OF FEMALES HAVING INTIMAL BOLSTERS

Group	Total	Male	Female	Intimal bolsters (% males)	Intimal bolsters (% females)
Dock	24	12	12	68	39
Total BIH	204	122	82	60	51
BIH group comparable to Dock's	76	51	25	43	35

statistics. He states, for example, that "4 female babies (of 12) and 1 male (of 12) had no intimal cushions in any of the arteries sectioned." This clearly implies that in 66% of the females and in 8% of the males intimal thickening was entirely absent. At the same time he writes that "61% of the arteries from females but only 32% from the males had endothelium lying on the inner elastic membrane, with no trace of intimal thickening."

In our series 60% of 122 males and 51% of 82 females revealed either a musculo-elastic and/or an elastic hyperplastic layer in one or more of their coronary arteries. In the group comparable to that of Dock, 43% of 51 males and 35% of 25 females evinced varying degrees of intimal thickening. These percentages are not in agreement with those of Dock, possibly because of differences in material and in numbers. It is very difficult to compare results, since only 1 previous investigator has included data concerning the diagnoses and the site from which the sections of each coronary artery was taken. More-

2. The second point of interest is that in a selected group of 51 males and 25 females not more than 1 day old, whose deaths had followed either birth trauma or asphyxia, a difference between the male and female intima-media ratio means of 2.6 times the probable error of the means was obtained. This is considered a highly suggestive difference. The validity of this difference and of that in Dock's material must be determined by examination of greater numbers of hearts.

But whether or not a significant sex difference in thickness of coronary intima is demonstrated, the important unanswered question is: "What do these intimal thickenings mean?" Are they transient, reversible responses to intra-uterine and neonatal insults? Are they permanent changes which may represent prearteriosclerotic lesions? There is certainly a strong resemblance in some of these intimal thickenings to the so-called early adult arteriosclerotic lesion, for in the elastic hyperplastic layer collagen may be found. We did not attempt to demonstrate fat;

this should have been done. Furthermore, the distribution of these thickenings has been shown to be strikingly similar to that of the adult arteriosclerotic lesion. However, these infantile thickenings are still a far cry from the adult lesions. When adequate numbers of coronary arteries from patients of all age levels from birth to adult life have been studied carefully, the answer to this question should be available.

3. The third observation of interest is the rôle played by infections. In our material bronchopneumonia was most common. For the entire group, and particularly for the group more than 1 month old, the differences in means between the infection and non-infection groups is clearly significant. No other factor suggests itself as an explanation for these differences. These observations apparently confirm numerous earlier workers who noted intimal thickenings in patients dying of acute infectious diseases. However, since our newborn and early neonatal material is deficient in infectious diseases as a cause of death, and since so few of our older infants and children died

of causes other than infections, it is difficult to be certain that an inflammatory process alone is responsible for these more frequent and greater intimal thickenings. Again, only study of additional hearts from infants dying of acute infections and from young children dying of non-infectious causes will provide an adequate answer.

**Summary.** 1. Coronary intimal thickenings may be expected to occur in a large number of newborns, infants and children dying of various causes.

2. In a group of 51 males and 25 females less than 1 day old, dying of birth trauma and/or asphyxia, the mean difference in coronary intimal thickness between male and female is strongly suggestive if not actually significant.

3. The rôle of acute infections appears to be an important one in producing intimal thickenings in older infants and children.

4. The meaning of these intimal thickenings, particularly as concerns the subsequent development of coronary arteriosclerosis, remains to be clarified.

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# ESTROGENS IN URINE AND CYTOLOGY OF VAGINAL SMEARS AFTER THE USE OF AN ESTROGENIC CREAM

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THESE studies were undertaken to observe the effect of estrogen, administered by inunction, on the estrogen content of urine, and on the histological picture of vaginal smears. Some workers<sup>3</sup> have shown that estrogens, administered in sufficient amounts and by various routes, produce an increase in urinary estrogens and alterations in vaginal smears. These changes varied with such factors as dosage, frequency and routes of administration. Creams and ointments containing estrogenic material have been suggested for inunction,<sup>6</sup> and some results have been described following their use.

**Method.** For our studies a cream containing 3750 I.U. per  $\frac{1}{2}$  ounce of inert base was used,\* and patients were instructed to "rub in" approximately one-seventh of this amount into the skin of the face each evening.<sup>2</sup> Thus approximately +535 I.U. were applied per day.† It has been pointed out that frequent smaller doses, "given in successive fractions were more effective than the same dose given" at one time.<sup>1,4,5</sup> Before commencing the use of the cream, 24-hour urines were collected once each week, except during menstrual periods, and vaginal smears were likewise made at about the same time. A total of 14 patients were studied, ranging in age from 18 to 56. The number of each patient as listed in the tables and her age are these: (1) 18 years, (2) 22 years, (3) 23 years, (4) 30 years, (5) 34 years, (6) 35 years, (7) 39 years, (8) 42 years, (9) 44 years, (10) 44 years, (11) 44 years, (12) 46 years, (13) 51 years, and (14) 56 years.

Patient No. 13 had begun to have menopausal symptoms, although still menstruating irregularly, and patient No. 14 had ceased to menstruate 5 years before. In all a total of 196 urine specimens were collected, 57 before the use of the cream, and 139 during the period of cream use, and 184 vaginal smears were made. In addition 4 women were used as non-treated controls for 15 weeks, 60 urinary estrogen determinations and 60 vaginal smear examinations being made, as described above.

**Results.** The estrogen output figures are given in Table 1. The variations in output during the period of the use of the estrogen inunctions are not significantly different from those in the pre-inunction period or from those in the untreated controls.

The vaginal smear findings are set forth in Table 2. They also show no significant change as a result of treatment.

**Summary and Conclusion.** 1. The fluctuations in estrogen excretion in 4 untreated controls and in 14 patients, before and during the use of an estrogen cream by facial inunction were similar in pattern and not significantly different in amount. Likewise, their vaginal smears appeared to show no significant alteration in cytological cycles.<sup>3</sup> Therefore, in the amounts and by the method applied (3750 I.U. per week, or +535 I.U. daily) the estrogen cream does not appear to produce any systemic effect.

\* The estrogenic cream was supplied by Lehn and Fink Products Corporation through the courtesy of Dr. E. G. Klarman. It contains 3750 I.U. of natural estrogenic hormone, essentially estrone and estradiol, per  $\frac{1}{2}$  ounce of cream. The vehicle contained lanolin (anhydrous) 22%, petrolatum (white) 40%, petrolatum (yellow) 6%, cholesterol 1%, mineral oil (heavy) 20%, lecithin 0.5%, distilled water 10%, and perfume 0.5%.

† Previous studies suggest that only about 20% of the estrogenic material is absorbed upon inunction, hence, about 100 I.U. per day in our studies.

TABLE 1.—ESTROGEN OUTPUT IN THE URINE, EXPRESSED IN RAT UNITS PER 24 HOURS, IN CONTROLS AND IN PATIENTS BEFORE AND DURING ESTROGEN INJUNCTIONS  
ESTROGEN — R.U./24 HOURS.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Average of control
Control 1	<5	<5	<5	<5	<5	20.3	17	19	24	17	16	28	25	6.8	8.4	..	17
Control 2	18	17	34.6	35	10	15	23	30	33.3	10	17	19	21	7	16	..	20
Control 3	<5	12.2	9	21.5	10	12.5	14	7	22	10	<5	<5	22	12	18	..	11
Control 4	10	11	16.5	15.7	22	<5	<5	17	26.5	24.3	9	13	33.3	17	27	..	16
Patient 1	<5	<5	<5	<5	30	<5	14	21	8.2	9	<5	15	..	..	..	..	Average after cream
Patient 2	<5	16	12	<5	28	<5	16	<5	7	14.5	12	7.8	..	..	..	..	9
Patient 3	<5	<5	12	<5	28	11	<5	<5	7	4	10	7.8	..	..	..	..	7
Patient 4	<5	<5	20	<5	30	14†	<5	<5	20	<5	<5	9.2	..	..	..	..	11
Patient 5	<5	<5	8.3	7.5	<5	10	<5	<5	<5	10.7	<5	10	7	<5	..	..	7
Patient 6	<5	<5	33.3	7.4	<5	12.6	<5	10	20	9.9	<5	10	9	<5	..	..	10
Patient 7	11.1	33.3	10	<5	<5	12.4	27	20	11	<5	<5	<5	10	14	15	15	11
Patient 8	11	16.5	<5	<5	<5	10	21	13	<5	<5	20	<5	<5	10	<5	<5	10
Patient 9	33.3	<5	30	<5	7	8.8	11.8	20	<5	14	12	20	<5	<5	10	<5	9
Patient 10	10.8	<5	<5	14	<5	<5	8.4	<5	15	8.8	9.8	20	<5	<5	13	13.5	10
Patient 11	<5	15.4	20	33.3	<5	<5	10	15	17	<5	20	<5	6.8	14	8.4	..	7
Patient 12	<5	19.4	<5	<5	<5	<5	<5	8.5	9	10	8.5	<5	10	<5	<5	8.5	11
Patient 13	18	<5	<5	<5	12.1	8.5	20	10	15	<5	9.8	<5	10	<5	33	..	6
Patient 14	<5	14	20	<5	11.2	10	<5	7	9	<5	<5	<5	7.5	<5	9	..	..

† Average of control period.

\* Use of cream begun.

TABLE 2.—CYTOLOGY OF VAGINAL SMEARS IN CONTROLS AND IN PATIENTS BEFORE AND DURING ADMINISTRATION OF ESTROGENS BY INJUNCTION.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Control 1	EP	O	O	PrM	P	P	PoO	PoP	P	PrO	PoO	PrM	PrM	PoM	EP	16
Control 2	PoM	EP	P	PrO	P	EP	P	PrM	PoM	EP	PoM	P	PrM	PoM	EP	15
Control 3	PoM	EP	P	PrO	EP	EP	O	PoO	PrM	PrM	EP	EP	P	P	P	16
Control 4	PoM	EP	PrO	PrO	O	PoM	O	O	PrM	PrM	EP	EP	PrO	PoO	PrM	16
Patient 1	EP	P	PrM	P	PrM	PoM	EP	PrO	O	O	EP	PrM	..	..	..	16
Patient 2	O	PoP	PrM	EP	PrO	PrM	EP	P	P (?)	PoO	P	PoO	..	..	..	16
Patient 3	PoM	P	P	PoO	P	PrM	P	PrM	PoM	PoM	P	PoM	..	..	..	16
Patient 4	PoM	EP	P	PoO	P	P	P	PrM	PrM	PoM	PoM	PoM	..	..	..	16
Patient 5	PoM	O	P	PoO	PrM	PoM	O	PoO	PoM	O	O	O	PoM	..	..	16
Patient 6	PoM	PoM	P	PrM	PrM	PrM	PrM	PoO	PrM	PoM	PrM	PrM	PrM	PrM	PrM	16
Patient 7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
Patient 8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
Patient 9	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
Patient 10	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
Patient 11	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
Patient 12	M	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
Patient 13	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16
Patient 14	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	16

P = Proliferative  
EP = Early proliferativePrM = Premenstrual  
PoM = Post-menstrualPrO = Pre-ovulatory  
PoO = Post-ovulatoryO = Ovulatory  
M = Menstrualm = Menopausal  
\* Use of cream begun

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OBSERVATIONS CONCERNING THE INFLUENCE OF POTASSIUM UPON  
THE ACTION OF A DIGITALIS GLYCOSIDE (LANATOSIDE C)\*

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ALTHOUGH there is experimental and clinical evidence<sup>5,9,10,11</sup> to support the theory that potassium in physiologic excess tends to inhibit the action of digitalis, there is little known about their physiologic interrelationships.

Cattell and Goodell,<sup>4</sup> Cattell,<sup>3</sup> and Wood and Moe<sup>14</sup> found that ouabain or a digitalis glycoside induced a loss of potassium from the interior of both skeletal and cardiac muscle. Hagen,<sup>8</sup> however, found that only toxic doses of a digitalis glycoside led to a loss of potassium from the rabbit heart. Moreover Wedd<sup>12</sup> as well as Boyer and Poindexter<sup>1</sup> believed that therapeutic doses of digitalis actually increased the potassium content of the heart. Certainly it seems clear from a perusal of the literature that no experimental evidence exists which indicates that the physiologic action of digitalis is completely dependent upon its theoretical properties of changing the potassium content of muscle.

In the following communication, the results of our studies dealing with the interrelationships of potassium and a digitalis glycoside (Lanatoside C) are reported. These results appear to indicate that whereas the specific cardiac actions of digitalis are not due to changes in potassium economy, the toxic action of the drug may be due to its property of ridding the heart of potassium.

**Methods.** The embryonic duck heart was employed using the method described in preceding articles.<sup>6,7</sup> Briefly, this particular biologic preparation reacts to the presence

of sufficient digitalis glycoside by the exhibition of increased rate of beating, hypertonic contractility, A-V block and finally cessation of beating. The time of appearance of A-V block as well as the duration of beating are quantitatively commensurate with the concentration of glycoside present. These last phenomena allow remarkable reproducibility in experiments carried out at any constant concentration of digitalis glycoside.

Tyrode's solution was employed for the basic medium and changes in its potassium content were made either by removing or adding the chloride of this cation. Lanatoside C (derived from *digitalis lanata*) was used in all experiments in which a glycoside was added to the basic solution. Unless otherwise noted, the temperature of the solution containing the embryonic heart was maintained constantly at 34° C. It should be mentioned that if the temperature is elevated to 36°, many hearts spontaneously exhibit A-V block. This last phenomenon may be abolished by addition of excess KCl to Tyrode's solution. The rate of beating as listed in the tables was obtained 5 minutes after the immersion of hearts into test solutions.

The investigation was divided into a study of: (1) the effect of changes in potassium ion concentration upon the activity of the embryonic heart; (2) the effect of potassium upon the physiologic activity of digitalis glycoside; (3) the effect of digitalis upon the potassium content of the embryonic heart.

**Results. 1. THE EFFECT OF POTASSIUM UPON THE NORMAL EMBRYONIC DUCK HEART.** Embryonic hearts when placed in Tyrode's solution without potassium invariably continued to beat (see Table 1,

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A1), although weakly, for an average period of 29 minutes. The rate of beating, although initially rapid, became progressively slower so that after 15 minutes the rate was usually less than 50 beats per minute. This slowing of rate continued until finally the hearts stopped in systole. Of the 29 hearts, 21 (72.5%) exhibited A-V block after an average period of 14 minutes. These hearts differed from hearts exposed to a large quantity of digitalis glycoside in: (1) their relatively slow rate, (2) the absence of hypertonic contractions, and (3) the frequent absence of A-V block.

the rate of beating became progressively slower and weaker, although the duration of beating was not altered until a concentration of 200 mg. per 100 cc. of KCl was reached. At this latter concentration, the rate of beating was 12 per minute, the vigor of beating became markedly impaired and the duration of contractions lasted for only 11 minutes.

2. THE EFFECT OF POTASSIUM UPON THE ACTIVITY OF DIGITALIS GLYCOSIDE. The complete absence of potassium was found (see Table 1, B1) to accentuate markedly the action of digitalis glycoside upon the embryonic heart. Thus 11 hearts

TABLE 1.—THE EFFECT OF VARIATIONS IN CONCENTRATION OF POTASSIUM UPON NORMAL EMBRYONIC HEARTS AND UPON THOSE EXPOSED TO DIGITALIS GLYCOSIDE.

	K conc. (mg. %)	No. hearts	Size of hearts*	Rate	A-V block (No.)	Onset of A-V block (mins.)	Rhythm	Duration of contractions (mins.)
<i>A. No Digitalis Glycoside Present</i>								
(1)	0	29	29	86	21	14	Irreg.	29
(2)	5	15	27	59	7	26	Reg.	Over 60
(3)	10	8	26	56	0	..	"	"
(4)	20†	15	28	59	0	..	"	"
(5)	100	12	29	51	0	..	"	"
(6)	125	5	25	29	0	..	"	"
(7)	150	10	25	19	0	..	"	"
(8)	200	5	28	12	0	..	"	11
<i>B. With Digitalis Glycoside (0.001 Mg. per Cc.)</i>								
(1)	0	11	28	105	11	5	Irreg.	17
(2)	5	15	27	90	15	7	"	22
(3)	10	24	28	94	24	7	"	22
(4)	20‡	18	31	90	18	11	"	22
(5)	100	17	26	58	14	33	"	47
(6)	125	10	27	27	0	..	Reg.	46
(7)	150	11	25	31	0	..	"	41
(8)	200	5	28	12	0	..	"	11

\* Equals the diameter in mm. of vascular sinus surrounding the embryo.

† Equals a control solution of ordinary Tyrode's solution.

‡ Equals a control solution of ordinary Tyrode's solution plus 0.001 mg. of digitalis glycoside per cc.

Hearts immersed in Tyrode's solution containing only 5 mg. per 100 cc. of potassium chloride beat weakly but continued to contract for over 60 minutes. Seven of the 15 hearts (see Table 1, A2) exhibited intermittent A-V block after an average period of 26 minutes.

Hearts placed in Tyrode's solution containing 10, 20 and 100 mg. per 100 cc. of KCl showed no essential differences in their cardiodynamics. However, when hearts were placed in higher concentrations of KCl (see Table 1, A 6, 7, 8),

immersed in Tyrode's solution without KCl but containing 0.001 mg. of glycoside per cc. exhibited A-V block after an average period of 5 minutes and ceased to beat after 17 minutes—a much stronger effect of glycoside than obtained in ordinary Tyrode's solution (see Table 1, B4).

Hearts placed in Tyrode's solution containing the same amount of glycoside but either 5 or 10 mg. per 100 cc. of KCl reacted as did hearts exposed to glycoside in ordinary Tyrode's solution except for

the more rapid occurrence of A-V block (compare Table 1, B2, 3 and 4).

When excess KCl was added to Tyrode's solution, however, the activity of the glycoside was inhibited markedly. Seventeen hearts exposed to 0.001 mg. of glycoside per cc. of Tyrode's solution containing 100 mg. per 100 cc. of KCl continued to beat at a rate apparently uninfluenced by the glycoside. Moreover (see Table 1, B5), only 14 of the 17 hearts (82%) exhibited A-V block and then only after an average period of 33 minutes. These same hearts also continued to beat for an average period of 47 minutes. It should be mentioned at this point that preliminary

Although these studies indicated that potassium inhibited the action of digitalis glycoside, such inhibition was usually accompanied by a marked reduction in rate of beating. Preliminary studies had indicated that when the rate of beating was depressed to an equal degree by lowering the temperature of the fluid bathing the hearts to 24° C., an inhibition of the action of digitalis glycoside occurred, which, although not as drastic as noted in the above cited experiments, nevertheless suggested that at least part of the inhibition of glycoside by excess potassium was due to the depression of the heart rate by the latter. However, potassium was found

TABLE 2.—THE BEHAVIOR OF HEARTS IN TYRODE'S SOLUTION AFTER PREVIOUS EXPOSURE TO DIGITALIS GLYCOSIDE AND EXCESS POTASSIUM

No. hearts	Size of hearts*	Rate	A-V block (No.)	Onset of A-V block (mins.)	Rhythm	Duration of contractions (mins.)
<i>A. Control Hearts After Previous Exposure to Digitalis Glycoside (0.001 Mg. per Cc.) for 5 Minutes</i>						
14	29	81	14	11	Irreg.	27
<i>B. Hearts After Previous Exposure to KCl (125 Mg. %) for 5 Minutes and Then to Digitalis Glycoside (0.001 Mg. per Cc.) for 5 Minutes</i>						
21	30	90	11	23	Reg.	55
<i>C. Hearts After Previous Exposure to KCl (125 Mg. %) and to Digitalis Glycoside (0.001 Mg. per Cc.) Together for 5 Minutes</i>						
16	31	87	9	28	Reg.	Over 60
<i>D. Hearts After Previous Exposure to Digitalis Glycoside (0.001 Mg. per Cc.) for 5 Minutes and Then to KCl (125 Mg. %) for 5 Minutes</i>						
15	31	90	11	34	Reg.	Over 60

\* Equals the diameter in mm. of the vascular sinus surrounding the embryo.

studies had shown that the same concentration of KCl would prevent completely the cardiac effects of smaller amounts of glycoside (*e. g.*, 0.00001 mg. per cc.). When these results were compared to those obtained in hearts exposed to the same amount of glycoside in ordinary Tyrode's solution, it became obvious (compare Table 1, B4 and 5) that the glycoside had been inhibited by the excess potassium. At higher concentrations of KCl in Tyrode's solution, the action of glycoside was even more retarded (see Table 1, B6, 7 and 8), as judged by the absence of increased rate of beating, A-V block and the prolongation of the duration of beating.

to inhibit digitalis even at rapid rates of heart beating as was shown by the following experiment. Fourteen control hearts were placed for 5 minutes in normal Tyrode's solution containing 0.001 mg. of glycoside per cc., and then transferred to pure Tyrode's solution. Hearts so treated (see Table 2, A) exhibited A-V block 11 minutes after being placed in the second solution and ceased after 27 minutes. When 16 hearts were exposed for the same amount of time to the same amount of glycoside in Tyrode's solution containing 125 mg. per 100 cc. of KCl, the hearts beat as rapidly as the control hearts (see Table 2, C) when they were transferred to the second Tyrode's solution. Never-

theless, only 9 of them (56%) exhibited A-V block and then only after an average period of 28 minutes. Moreover, all of these hearts continued to beat for over 60 minutes. These results allowed little doubt that the inhibition of digitalis glycoside effected by excess potassium was certainly not due exclusively to the latter's ability to depress the rate of beating.

Further studies indicated that potassium was able to inhibit the action of digitalis glycoside regardless of whether the heart was exposed to excess potassium before or after its contact with digitalis glycoside. Thus when 21 hearts were immersed for 5 minutes in Tyrode's solution containing 125 mg. per 100 cc. of KCl and then transferred for 5 minutes to a solution containing 0.001 mg. of glycoside per cc. (see Table 2, *B*), only 11 (52%) exhibited A-V block when transferred again to normal Tyrode's solution. When these results were compared to those obtained on the control hearts (compare Table 2, *A*, *B*), it can be seen that preliminary administration of KCl protected the hearts against digitalis. Likewise, when 15 hearts were first placed for 5 minutes in Tyrode's solution containing 0.001 mg. of glycoside per cc., then transferred to Tyrode's solution containing 125 mg. per 100 cc. of KCl for 5 minutes, and finally transferred to normal Tyrode's solution (see Table 2, *D*), only 11 of the 15 hearts (73%) exhibited A-V block after an average period of 34 minutes. Moreover, these hearts beat for over 60 minutes.

3. THE EFFECT OF DIGITALIS GLYCOSIDE UPON THE POTASSIUM CONTENT OF THE EMBRYONIC HEART. (a) *Toxic Concentration of Glycoside (0.001 Mg. per Cc.)*. Nineteen hearts were immersed in Tyrode's solution containing 0.001 mg. of glycoside per cc. Each of these hearts promptly increased their rate of contractions, exhibited A-V block within 11 minutes and ceased beating after an average period of 22 minutes. After they had ceased to beat, they were transferred to Tyrode's solution containing 125 mg. per 100 cc. of KCl. Approximately 12 minutes after

this transfer, each of the hearts began to beat again and continued to do so for over 45 minutes although the rate of beating averaged only 30 beats per minute (apparently due to the high KCl concentration). However, A-V block appeared as soon as the hearts began to contract again and it never disappeared despite the duration of beating. Thus, although a high concentration of KCl was able to initiate beating in a heart stopped by a toxic amount of glycoside, it was not able to abolish the A-V block.

(b) *Therapeutic Concentration of Glycoside (0.00001 Mg. per Cc.)*. In order to determine the possible effect of a minute amount of glycoside (which previous studies<sup>11</sup> had shown ineffective in hastening the cessation of beating of embryonic hearts) upon the potassium content of the hearts, 10 control hearts beating in normal Tyrode's solution and 23 hearts beating in Tyrode's solution containing 0.00001 mg. of glycoside per cc. were observed until all of them ceased beating.

It was found that whereas none of the control hearts exhibited A-V block, 15 of the 23 hearts exposed to glycoside, exhibited A-V block after an average period of 56 minutes. The control hearts finally ceased beating after an average period of 184 minutes. Hearts exposed to glycoside ceased beating after an average period of 190 minutes. Transfer of both the control hearts and those exposed to glycoside to Tyrode's solution containing 125 mg. per 100 cc. of KCl was not followed by a resumption of beating in any heart of either series. These findings suggested strongly that, although the amount of glycoside used was able to produce A-V block in hearts exposed to it, it did not appear to lead to a significantly greater loss of potassium from these same hearts, as judged by the duration of beating.

In a previous section it was found that hearts beating in Tyrode's solution without potassium usually exhibited A-V block and ceased beating after an average period of 29 minutes. These abnormal cardiodynamics supposedly were due to a

gradual loss of KCl from the embryonic hearts. Furthermore, it was pointed out that the behavior of these hearts in such a solution was qualitatively different from hearts exposed to glycoside. In order to investigate this further, 10 hearts were exposed to a therapeutic amount of glycoside (0.00001 mg. per cc.) in Tyrode's solution containing no KCl. If small amounts of glycoside acted to withdraw potassium from the heart, these latter hearts should cease much sooner than hearts immersed in Tyrode's solution which was of normal character except for the complete absence of KCl. However, it was found that the 10 hearts exposed to glycoside in Tyrode's without KCl continued to beat for an average period of 30 minutes. When this duration of beating was compared with that of hearts beating in Tyrode's without KCl (see Table 1, A1), it was found that there was no significant difference. This finding further confirmed the above observation, that an amount of glycoside (0.00001 mg. per cc.) which could produce A-V block probably did not withdraw potassium from the embryonic duck heart.

**Discussion.** The preceding observations strongly suggested that much of the confusion concerning the relationship of potassium and digitalis might be due to overlooking the fact that potassium, regardless of the presence or absence of digitalis, acts as a cardiac depressant. Thus, Wiggers *et al.*<sup>13</sup> clearly showed that the ventricular fibrillation sometimes occurring in dogs during operative procedure could be abolished by the coronary perfusion of potassium. Likewise, Sampson and Anderson<sup>11</sup> showed that the administration of potassium to patients suffering from cardiac arrhythmias frequently led to the elimination of the latter regardless of the cause of the arrhythmia. Castle<sup>2</sup> in confirming the findings of Sampson and Anderson also pointed out that extrasystoles occurring spontaneously or after insulin hypoglycemia in patients who had not received digitalis might disappear after potassium administration. In our studies,

regardless of whether A-V block was initiated by an elevation of temperature or by the administration of digitalis glycoside, it was inhibited in its onset by excess potassium. Furthermore, excess potassium was able to inhibit the A-V block produced by a quantity of glycoside which in itself was found incapable of causing a withdrawal of potassium from the heart. These facts suggested that excess potassium was able to inhibit the effect of digitalis glycoside in part at least because of its own intrinsic power to depress the irritability of the heart. However, excess potassium also was found to inhibit the effects of large amounts of digitalis glycoside in a specific manner, presumably by supplying the heart with potassium when the latter was losing its own because of the toxic effect of digitalis glycoside. This last observation was essentially in accord with the experimental findings of Hagen,<sup>8</sup> and Wedd,<sup>12</sup> and in part with those of Wood and Moe<sup>14</sup> who also found that toxic amounts of digitalis caused the heart to lose potassium. The observation also might explain the abolition of arrhythmias in overdigitalized patients after the administration of potassium.<sup>10</sup>

Thus it appears that the potassium ion is able to inhibit the actions of digitalis upon the heart by: (1) itself depressing the irritability of the heart, and (2) offsetting the loss of potassium from the heart which occurs whenever the latter is exposed to large or toxic amounts of digitalis.

**Summary.** 1. The effects of different concentrations of potassium upon the normal embryonic duck heart were studied. It was found that the absence of potassium led to arrhythmias and early cessation of beating. Excess potassium conversely, depressed heart action.

2. The absence of potassium was found to enhance the effects of a digitalis glycoside (Lanatoside C), whereas an excess of potassium inhibited the actions of the same drug.

3. Only large or toxic amounts of digitalis glycoside were found to cause a probable loss of potassium from the heart.

Excess potassium was effective in inhibiting this process.

4. The results of the entire study indicated that excess potassium was able to inhibit the actions of digitalis glycoside

by the following mechanisms: (1) by itself depressing the irritability of the heart, and (2) by serving as a source of potassium to a heart apparently losing it after exposure to toxic amounts of digitalis.

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# PROLONGED HYPERCALCEMIA AND METASTATIC CALCIFICATION OF THE SCLERA FOLLOWING THE USE OF VITAMIN D IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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WITHIN the past few years a number of reports have appeared in the medical literature regarding the harmful effects of prolonged administration of large amounts of irradiated ergosterol. Such effects have been reported mainly in patients suffering from rheumatoid arthritis. The toxic reactions are reported to be either acute or chronic. The acute reactions consist of nausea, vomiting, abdominal pain, anorexia and diarrhea, all of which promptly disappear when vitamin D is withdrawn. The chronic symptoms are usually those related to the presence of metastatic calcifications and appear secondarily to hypercalcemia.

The symptoms of acute toxicity from vitamin D appear quite early in the course of therapy, and seem to be influenced by the amount of vitamin D and calcium ingested.<sup>5,23</sup> There also seems to be considerable individual variation among patients regarding the amount required to produce intoxication.<sup>14</sup> It has been indicated by Lewis<sup>13</sup> that vitamin D given in milk may have ten times the potency of that given in oil. Bauer<sup>2</sup> has suggested that the lack of toxicity reported by some observers following the administration of large doses of ergosterol may be accounted for on this basis. Tumulty and Howard<sup>23</sup> report 2 patients in whom gastro-intestinal symptoms appeared about 2 weeks following the daily ingestion of 750,000 international units of irradiated ergosterol. In a patient reported by Freeman, *et al.*,<sup>11</sup> symptoms of acute toxicity appeared after

taking approximately 300,000 international units for a period of 6 weeks.

Diminution in renal function is frequently observed following the excessive ingestion of vitamin D. Patients with normal renal function prior to taking vitamin D have shown albuminuria, hematuria, and retention of non-protein nitrogen components after receiving large doses for a prolonged period of time.<sup>7,8,11,23</sup> Steck, *et al.*,<sup>20</sup> indicate that the kidney is exceptionally vulnerable to the action of vitamin D, and that diminution in renal function might be regarded as a contraindication to administering large amounts of this vitamin.

Calcification of soft tissues may also appear following the prolonged administration of vitamin D. These may be detected clinically as localized, painful swellings around the joints,<sup>8,11</sup> or as radiographically opaque areas in muscles, blood-vessels, kidney, and tendon attachments. It has been demonstrated repeatedly that experimental animals can be killed by administering large doses of irradiated steroids and that the outstanding pathological finding in these animals is diffuse metastatic calcification involving especially the arterial system and the kidneys. Mulligan<sup>14</sup> and Bauer<sup>2</sup> both reported cases showing metastatic calcification following the prolonged administration of vitamin D. These cases at autopsy disclosed microscopic calcification in the endocardium, arteries, kidneys, lungs, tendons, dura and subcutaneous tissues. According

to Steck, *et al.*,<sup>20</sup> the subcutaneous tissue calcification in some patients may disappear after discontinuing the administration of vitamin D. Shelling and Asher<sup>17</sup> indicate that the metastatic calcifications in the tissues are apt to develop at sites of local injury.

The literature pertaining to vitamin D and its relation to calcium and phosphorus metabolism in experimental animals is extensive; that on human subjects is more limited. Dreyer and Reed<sup>9</sup> found the concentration of serum calcium to be greatly increased in humans receiving large doses of vitamin D; on the other hand, Wyatt and his colleagues<sup>24</sup> reported only slight increases. It would appear that perhaps other factors, in addition to vitamin D, may be responsible for the development of the increased concentration of serum calcium. Bauer<sup>2</sup> has called attention to great individual variations from patient to patient in the dose required to produce deleterious effects. Several investigators<sup>5,12</sup> have shown that the degree of hypercalcemia produced by irradiated ergosterol is to an extent dependent upon the amount of calcium ingested. It is noteworthy that many of the patients who showed undesirable effects following administration of vitamin D, had in addition, received abnormally large amounts of calcium.<sup>2,5,11</sup>

**Case Report.** The patient was admitted to the medical wards of the Hospital of the University of Pennsylvania on January 3, 1946. Five years prior to admission she first noticed arthritic pains primarily in her hands but also involving her shoulders, elbows, and knees. At this time her physician began treatment with a proprietary brand of vitamin D.\* She continued taking this preparation for a period of 3½ years, taking an average dose of 2½ capsules daily (125,000 units).† From close questioning it was estimated that our patient took approximately 4 capsules (200,000 units) daily for the first year, 3 capsules (150,000 units) daily

for the second year, 2 capsules (100,000 units) daily for the third year, and 1 capsule (50,000 units) daily for the remaining 6 months. All medication had been stopped 8 months prior to admission.

One and one-half years before admission she first noted pain in the region of the left sacro-iliac joint and left ischial tuberosity which radiated down the left leg along the distribution of the sciatic nerve. Several weeks before admission she developed severe pain about the right knee located especially over several nodules that had developed in this area. She had lost 20 pounds in weight during the year preceding admission. The past medical, family and social histories were not contributory.

Physical examination revealed a thin, apprehensive, asthenic, elderly woman. Blood pressure was 140/90 mm. of Hg. Examination of the heart and lungs revealed no lesions. The liver was palpable 2 to 3 cm. below the right costal margin. The left iliac crest was abnormally prominent and irregularly nodular. Exquisite pain could be elicited by pressure over the left sacro-iliac joint and over the left ischial tuberosity. There was limitation of motion at the left hip owing to pain. Marked tender hyperostosis with many exostoses were found at the ends of both bones forming the knee joints. Over the distal interphalangeal joint of the left thumb there was a soft tissue swelling in which could be felt several hard freely movable bodies. All the interphalangeal joints and metacarpophalangeal joints showed bony enlargement with some limitation in flexion.

External examination of the eyes disclosed equal fissures, clear lids and good lid function. Ocular tension was regarded as normal. Pupils were regular and reacted to light and near stimuli. Ocular movements, both dysjunctive and conjugate, were full. The conjunctivae were clear except in the fissural areas close to the corneas both on the nasal and temporal sides. Several flecks of highly reflecting, irregular, solid material were seen in this area which were not foamlike and were definitely calcareous to touch. Underlying these deposits were areas of "flesh colored" depositions approximately tri-

\* Ertron, which according to the manufacturer is "electrically activated vaporized ergosterol prepared by the Whittier process."

† According to the manufacturer "each capsule of Ertron contains 5 mg. of activation-product having a potency of not less than 50,000 U. S. P. units of vitamin D."

angular in shape, which were stony hard when scraped. On both the nasal and temporal sides of each cornea, in the fissural zone were areas of irregular, superficial, white, granular opacities. (Figure 1.)

By slit lamps these opacities were found to be in the superficial part of the cornea between the epithelium and the most anterior stroma. These opacities seemed to be spreading toward the center of the cornea. The lens showed large spokes and spicules in the cortical area.

per 100 ml. Only 20% of phenolsulphone-phthalein was excreted in 45 minutes.

Roentgen examinations of the bones revealed degenerative arthritic changes of both knees, hypertrophic changes in the lumbar spine and lumbosacral joint, asymmetry of the pelvis with demineralization, and some calcification of the blood-vessels posterior to the femur. An intravenous urogram revealed marked diminution in the excretion of neo-iopax by both kidneys. No structural abnormalities of the kidneys were noted.

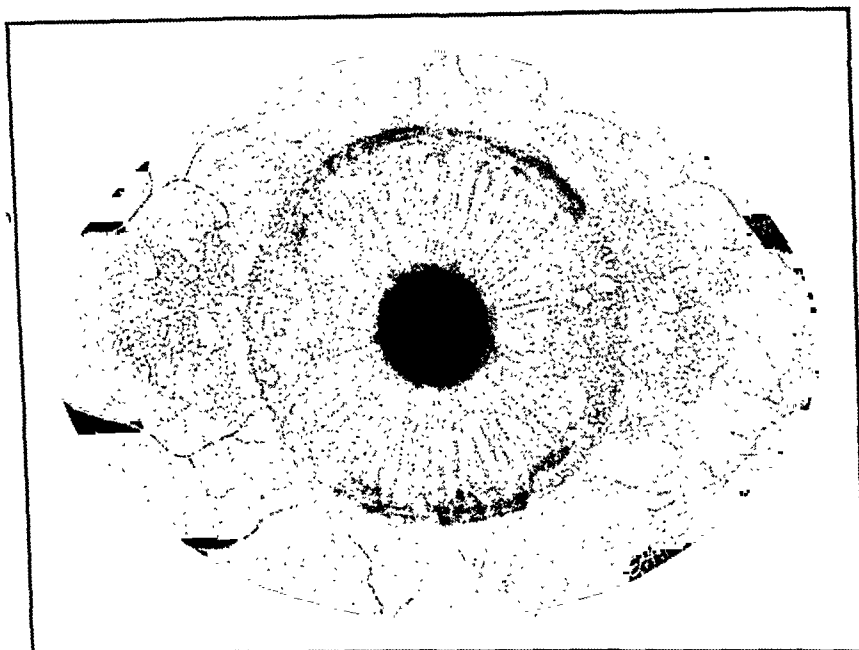


FIG. 1. Calcareous infiltration into conjunctiva and cornea.

**LABORATORY STUDIES.** The blood count revealed 3.6 million erythrocytes per cmm.; 6000 leukocytes per cmm., and a normal differential count. The hemoglobin concentration was 10.9 gm. per 100 ml.; fasting blood sugar, 73 mg. per 100 ml.; blood urea nitrogen, 28 mg. per 100 ml.; total serum protein, 6.3 gm. per 100 ml.; serum albumin, 4.3 gm. per 100 ml.; and serum globulin, 2 gm. per 100 ml. The concentration of serum calcium was 12.8 mg. per 100 ml.; serum alkaline phosphatase, 5.5 units (Shinowara, Jones and Reinhart); serum cholesterol, 295 mg. per 100 ml. Serological tests for syphilis were negative. Spinal fluid examination, including cells, protein, serological and colloidal gold tests, were not remarkable. The semi-quantitative Sulka-witch test for the estimation of calcium in the urine yielded approximately 200 mg.

**CALCIUM BALANCE MEASUREMENTS.** Measurements of the calcium balance were undertaken on our patient following the plan described by Bauer and Aub.<sup>4</sup> The analysis of samples of a hashed daily diet yielded 160 mg. of calcium and 768 mg. of phosphorus. Sufficient calcium lactate was given orally so that the total calcium ingested amounted to 1 gm. daily. After the patient had been placed on this regimen for one week to permit adjustment, collections were obtained for analysis. The period of study was divided into periods of 3 days, during which all urine and feces were collected and pooled separately. The limit of each 3-day period for the collection of feces was determined by the appearance of carmine in the stool. Samples of serum from venous blood were collected at the beginning of each 3-day period and at the end of the study. The



amount of calcium contained in each pooled specimen of urine and feces was obtained by the method of Shohl and Pedley<sup>18</sup> and the amount of the inorganic phosphorus of these specimens, by the method of Tisdall.<sup>22</sup> Methods for the analysis of the serum components are the same as those previously reported.<sup>21</sup>

continuing vitamin D, the concentration of serum calcium had returned to within the normal range of values. All other concentrations of serum electrolytes were within normal limits excepting serum magnesium which was decreased initially, at the time when the serum calcium was

TABLE 1.—CALCIUM BALANCE STUDIES

Periods (3-day)	Ca food intake per period, mg.	Ca lactate as Ca/period, mg.	Total Ca intake, gm.	Calcium output		Total Ca output, gm.	Calcium balance, gm.	Percent total Ca excreted in urine
				Urine	Feces			
I	424	2571	2.995	0.428	2.375	2.803	+0.192	15
II	580	2571	3.151	0.388	3.200	3.588	-0.437	11
III	498	2571	3.069	0.381	3.675	4.056	-0.987	9
				Total			-1.232	
IV	298	0	0.298	0.338	0.144	0.479	-0.181	81

TABLE 2.—SERUM COMPONENTS

Date, 1946	Total base mEq/L	Calcium mg. per 100 ml	Magnesium mEq/L	Inorganic phosphorus mg./100 ml.	Chloride mEq/L	Total CO <sub>2</sub> vol. %	Total pro- tein gms. per 100 ml.	Total cholesterol mg./100 ml.	Blood urea nitrogen mg./100 ml.	Serum uric acid mg./100 ml.	Blood sugar mg./100 ml.
Jan. 6	..	14.3	..	4.3	..	..	6.8	294	28	..	73
Jan. 18	..	13.4	1.6	4.1	..	..	6.8	..	29	..	..
Jan. 4	..	12.7	..	..	..	..	..	..	..	..	..
Mar. 21	149.0	12.1	1.9	4.1	101.7	56	6.5	..	26	4.2	..
May 11	150.0	10.9	1.9	4.2	101.9	..	5.8	278	33	..	..
Normal values	142.0 to 149.0	9.0 to 11.0	1.8 to 2.2	3.2 to 4.3	98.5 to 104.5	60 to 71	5.9 to 7.0	150 to 190	8 to 15	2.0 to 4.0	70 to 100

**Results.** The results of the calcium balance studies are given in Table 1. It will be seen that excepting for Period I, in spite of an adequate calcium intake, our patient was in negative calcium balance. On an adequate intake of calcium 9 to 15% of the calcium ingested was excreted in the urine. On a low intake of calcium (Period IV) the fecal calcium decreased to 0.144 gm. and 81% of the total calcium was excreted in the urine.

The results of estimations of the serum components are given in Table 2. The concentration of the serum calcium was elevated on admission to the hospital and remained increased during the following 11 weeks, although vitamin D therapy had been stopped 8 to 11 months previously. On reexamination 13 months after dis-

increased. The concentration of blood urea nitrogen, which was elevated at the time of admission, was found to be higher on reexamination.

**Discussion.** It would appear from these studies that the patient probably suffered from the prolonged unsupervised administration of vitamin D. Massive doses of vitamin D have been used in the treatment of arthritis during the past decade, and the clinical reports, until recently, have implied that such administration produced no harmful effects. The studies of Danowski, Winkler and Peters,<sup>8</sup> however, indicated that this was not necessarily the case and called attention to 2 patients who had received vitamin D for the treatment of arthritis and whose

clinical courses were somewhat analogous to that of our patient.

Freeman, Rhoads and Yeager<sup>11</sup> report 2 patients who had received massive doses of vitamin D for periods of 5 months and 6 years respectively. These authors emphasized the impairment of renal function as evidence of vitamin D toxicity in their patients. Our patient also exhibited diminished renal function as indicated by: (1) elevated blood urea nitrogen, 28 mg. per 100 ml.; (2) increased serum uric acid, over 10 mg. per 100 ml.; (3) decreased excretion of phenolsulphonephthalein, with 3% excreted in 15 minutes and 28% in 2 hours; (4) diminished excretion of neopax.

in our patient. (3) Zonular or band-shaped dystrophy occupies the external layers of the cornea as do the eye lesions in the present patient and is thought to be at least in the later stages an example of calcareous degeneration. The ocular findings in this patient resemble those of zonular dystrophy. In addition, this patient displayed a gritty-stony-scleral deposit. It therefore seems likely that these ocular changes represent calcific deposition.

It is quite likely that these abnormalities of the cornea and conjunctiva in a patient with hypercalcemia can very well be attributed to calcific deposits. It is realized that by clinical appearance they could be lipoid or hyaline in nature and that chemical analysis would have been helpful. Scrapings of the flesh colored lesions in the deep bulbar conjunctiva and sclera indicated the presence of calcium.

The question obviously is raised as to whether persistence of hypercalcemia 8 months after our patient stopped taking vitamin D is due to the continuance of vitamin D effect. Support for this opinion is suggested by the calcium balance studies. On the Bauer and Aub diet when our patient ingested only 298 mg. of calcium in 3 days, the excretion of calcium in the urine remained essentially the same as the amounts excreted on a normal intake of calcium, although the excretion of calcium in the feces was greatly diminished. These alterations in the route of calcium excretion are similar to those observed by Bauer, Albright and Aub<sup>3</sup> in individuals on low intake of calcium and receiving large doses of vitamin D. In this connection it should be noted that similar hypercalcemia was also reported by Danowski, Winkler, and Peters.<sup>8</sup> In one of their patients the hypercalcemia persisted for 1½ years after discontinuance of the vitamin D medication.

The ocular lesions which are illustrated in Figure 1 suggest three diagnostic possibilities: (1) Arcus senilis which, however, can be excluded as it usually starts at either the upper or lower pole of the cornea and the site of infiltration is most often in the deep parenchyma. (2) White, limbus girdle can also be ruled out as it spreads concentrically around the cornea and does not show the dark areas as seen

It would seem obvious that patients receiving vitamin D for the treatment of arthritis should not be permitted to continue treatment on their own initiative. Measurement of serum calcium should be made at frequent intervals and the administration of vitamin D should be stopped if hypercalcemia develops. In addition, it might be worth emphasizing that in any patient having an unexplained hypercalcemia, careful questioning might be made regarding the previous intake of vitamin D. It would also appear that the toxic effects from the administration of vitamin D perhaps may be more common than the paucity of reports may indicate.<sup>8</sup>

The introduction of vitamin D in the therapy of arthritis followed the chance finding that patients receiving this substance for allergic conditions showed a coincident improvement in arthritis<sup>15</sup>. Experimentally in rats the administration of vitamin D may produce either a decrease or an increase in bone ash depending upon the dose,<sup>6</sup> but there appears to be no correlation between alterations in the density of the skeleton or exostoses and clinical improvement in arthritis following

the administration of vitamin D.<sup>10,19</sup> Likewise abnormality in the calcium and phosphorus balance of patients with arthritis has not been demonstrated.<sup>16</sup> If there are any favorable effects of vitamin D in arthritis it would appear that they are probably unrelated to the metabolism of either calcium or phosphorus.

**Summary.** Studies of calcium metabolism are reported in an individual suffering from rheumatoid arthritis who had received large amounts of vitamin D for a period of

42 months. Although vitamin D had been discontinued 8 months previously, hypercalcemia persisted and on a low intake of calcium, a relatively high excretion of calcium was maintained in the urine. In addition, there was evidence of diminution of renal function. Calcium deposits into the sclera and cornea were prominent features. Our studies support the view that the administration of large doses of vitamin D may have a prolonged effect lasting over a period of months.

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## TULAREMIA TREATED WITH STREPTOMYCIN

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SINCE the early descriptions of tularemia between 1910 and 1920, many remedies have been used, including sulfonamides and penicillin. Until 1944 only 2 preparations had been classed as effective treatment; the antitularense serum, advocated by Foshay,<sup>1</sup> and bismuth sodium tartrate intravenously, advocated by Jackson.<sup>4</sup> In 1944, Heilman<sup>3</sup> published data on the treatment of experimental tularemia showing that mice could be protected from a lethal dose of *Pasteurella tularensis* by the subcutaneous administration of streptomycin. Since that publication, several investigators have reported the effectiveness of streptomycin in the treatment of this disease.<sup>2,5</sup>

This study reports favorable effects of streptomycin in the treatment of 5 patients with tularemia. In each case, the handling of wild rabbits was the source of infection. The 2 patients with the typhoidal type of the disease and 1 of the 3 ulceroglandular type were critically ill on admission.

**Method of Treatment.** The streptomycin, dissolved in normal saline, was given intramuscularly every 3 hours. In 2 cases the daily dose was 400 mg. In the other cases 800 mg. per day were administered.

**Case Reports.** CASE 1. S. S., a 59 year old obese housewife, began to have symptoms within 24 hours after she accidentally stuck a bone of a wild rabbit into her right thumb. These symptoms consisted of nausea, vomiting, chills and fever and extreme somnolence. She was admitted to the hospital 4 days after onset of symptoms. The findings at this time showed an elderly

woman acutely ill. Temperature 103.8° F. The only other significant findings were the ulcerative lesion on the thumb, markedly tender enlarged axillary nodes on the same side, and smaller epitrochlear nodes.

The patient was given a total of 500,000 units of penicillin intramuscularly during the first 3 days of hospitalization with no evidence of improvement. Streptomycin was started on the 5th hospital day, 0.4 gm. daily for 18 successive days, making a total of 7.2 gm.

She noted marked subjective improvement on the 2nd day of streptomycin therapy. The recovery was rapid; there was rapid decrease in the pain of the axillary nodes and a gradual reduction of the nodes to normal size by the 23rd hospital day, when she was discharged. No subsequent lymphadenopathy occurred. The agglutination titer for tularemia was negative for the first 8 days of the disease. Although the streptomycin was started during this negative period, the agglutination titer gradually increased, reaching a peak of 1:2560 on the 28th day of the disease. The patient's subsequent course has been uneventful. Figure 1 summarizes certain features of the clinical course.

CASE 2. W. J., a 28 year old butcher, punctured his left middle finger with a rabbit bone 2 weeks before the onset of weakness, anorexia, malaise and general muscular aches. He was admitted to the hospital during the 3rd week of disease, not acutely ill. The clinical findings indicated an ulceroglandular type of tularemia. An axillary node was enlarged (3 by 2 cm.), tender but non-fluctuant. Treatment consisted of streptomycin, 0.8 gm. daily for 4 days and 0.4 gm. for 3 days.

The fever subsided rapidly; there was

rapid healing of the primary lesion and the axillary node had decreased to less than 1 cm. in diameter by the 17th hospital day. He was discharged to be followed in the clinic.

The patient was seen again 18 days after discharge. At this time there was a large fluctuant mass at the site of the previous lymphadenopathy. The leukocyte count was 13,400, although the temperature was normal. Aspiration yielded 40 cc. of grayish brown pus. The patient was again given streptomycin, 1.2 gm. daily. Animal inoculations and cultures were done on the pus with negative results. Eight days later,

and slight nuchal rigidity. Available history indicated sudden onset of headache, fever, low back pain of 4 days duration. The examination showed the patient critically ill, dullness and râles were present at the right base but no lymphadenopathy nor ulcerations were present. The lumbar puncture showed a pressure of 220 mm. of water but the cell count was normal. During the first 3 days she was treated with penicillin and salicylates without improvement. The temperature reached 106° F. on the 3rd hospital day. At this time streptomycin was started empirically, 100 mg. every 3 hours.

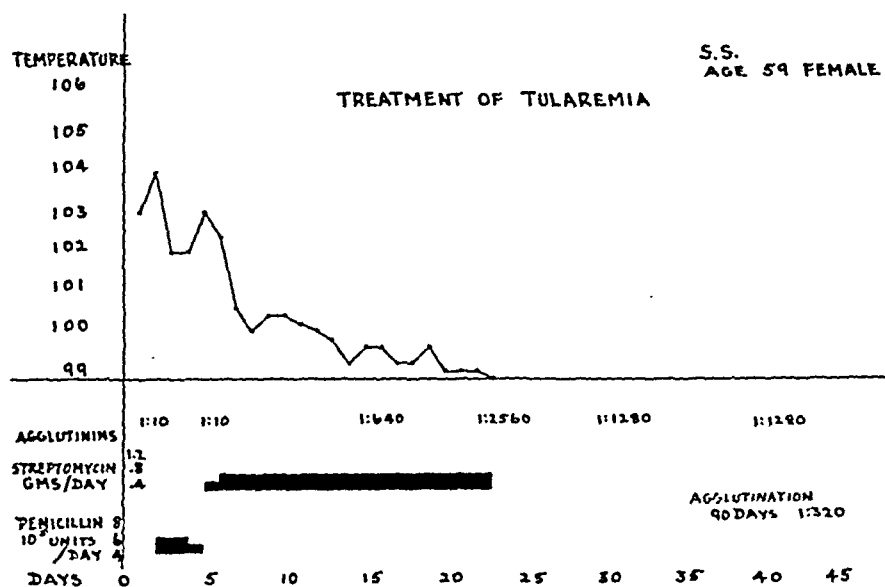


Fig. 1

35 cc. of similar pus were removed from the same site and this time 50 mg. of streptomycin in saline was injected into node. The node diminished in size and became indurated and the patient was again discharged on the 20th hospital day. Twelve days later the node had again enlarged and was fluctuant. It ruptured spontaneously. Although the node drained for a considerable period, convalescence was otherwise uneventful (Fig. 2). The initial agglutination, taken in the 3rd week of the disease, was positive 1:1280. At no time did the titer exceed that dilution.

**CASE 3.** A. W., a 48 year old housewife, was admitted to the hospital in a state of delirium, and with temperature 105.6° F.

On the 2nd day of streptomycin therapy the temperature dropped to 99.6° F., at which time the delirium cleared. During the succeeding 14 days of streptomycin therapy, all symptoms except slight weakness disappeared but the fever continued to fluctuate. On the 16th day of streptomycin therapy the possibility of streptomycin fever was considered and the drug was discontinued for 9 days. Since the fever continued during this 9 day interval, streptomycin was started again, 50 mg. every 3 hours intramuscularly, without significant effect on the fever (Fig. 3).

The agglutination for tularemia taken on admission was positive only in 1:40 dilution. After the delirium had cleared, a history of

handling wild rabbits was obtained, so additional agglutination tests were made. At this time a diagnosis of typhoidal tularemia with pneumonitis was made. On the 22nd day of the disease the titer was positive, 1:5120. In spite of a continued low grade fever, the patient remained symptom free, and was discharged at her request with rec-

tal temperature of 100° F. On subsequent visits she remained symptom free, but several weeks elapsed before the temperature became normal.

CASE 4. S. H., a 34 year old butcher, had been dressing wild rabbits daily for a 2 week period prior to the onset of symptoms. His initial symptoms were chills and fever

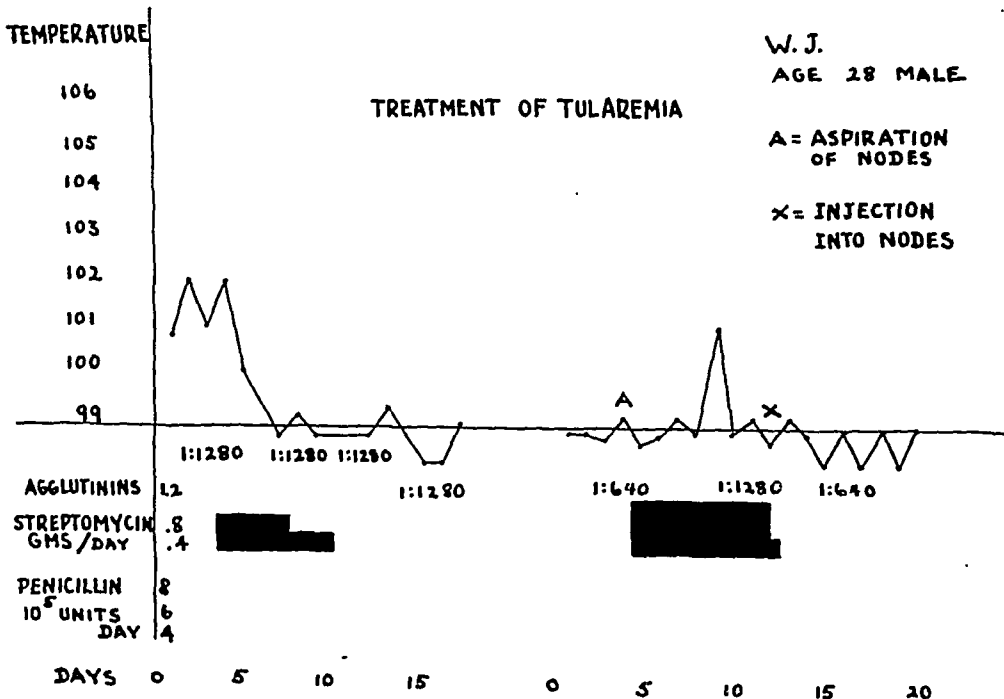


FIG. 2

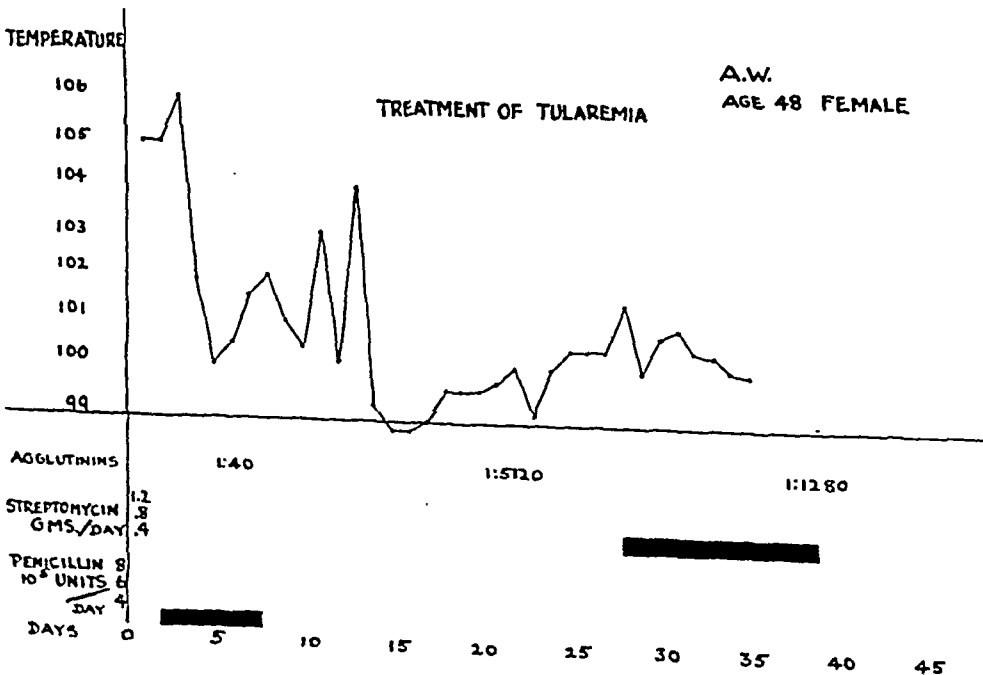


FIG. 3

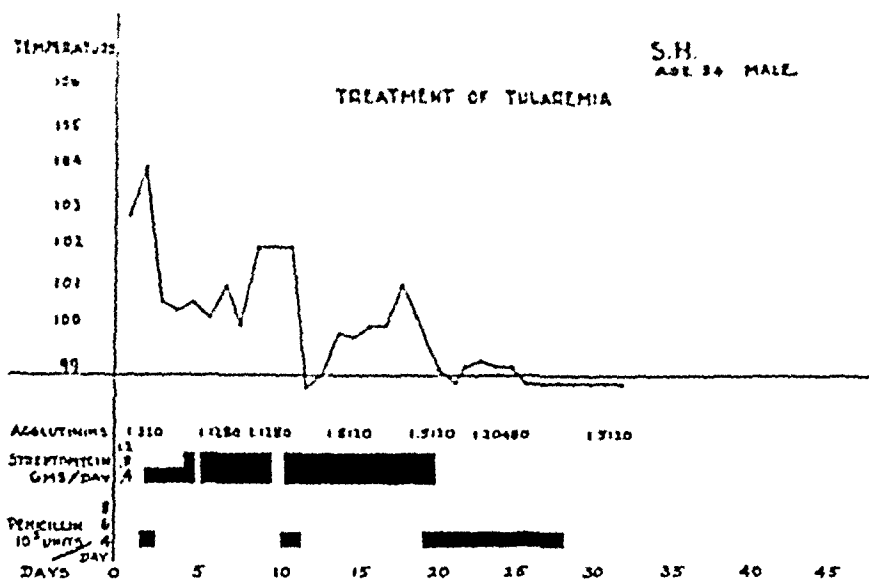


FIG. 4

Streptomycin intramuscularly was started on the 2nd hospital day, 50 mg. every 3 hours for 2½ days, at which time the dose was increased to 100 mg. every 3 hours because of the increasing delirium. In view of the alcoholic history the possibility of delirium tremens was considered and the patient was started on thiamin chloride, 200 mg. intramuscularly every 3 hours.

Within 2 days the delirium was much improved. The patient's course was uneventful except on 2 occasions when the temperature became elevated while the streptomycin was being given. In each instance the temperature dropped to normal with penicillin therapy (Fig. 4).

of 9 weeks but none of these physicians suspected the correct diagnosis. During this 9 week period she continued to have low-grade fever and occasional chills and severe headache. At the time of admission the primary lesion on the left thumb was still ulcerated and there was a mass of enlarged nodes in the left axilla which was exquisitely tender and distinctly fluctuant. In addition there were several lymphangitic nodules on the flexor surface of the left forearm. The admission temperature was 99° F., the leukocytes 10,500. The patient was 3½ months pregnant.

We decided to see whether the mass of axillary nodes could be resolved by systemic and

local streptomycin therapy without surgical drainage. She was given 100 mg. of streptomycin intramuscularly every 3 hours. On the 6th day of therapy, 100 mg. of streptomycin was injected directly into the node after aspiration of 300 cc. of pus. This procedure was repeated 3 times during the next 7 days, until we were convinced that no improvement was to be expected. At this time surgical drainage was instituted. The drainage continued for a short period but gradually disappeared as the surgical wound healed in several weeks. The lymphangitic nodules showed rapid healing, never reaching a stage of suppuration. The initial agglutination was positive, 1:1280, and con-

critically ill patients. One of the 2 patients with delirium showed complete clearing of the mental state within 36 hours after the streptomycin was started. The delirium in the 2nd patient was complicated by delirium tremens, but also showed rapid clearing with a combination of parenteral vitamins and streptomycin. The severe headache and somnolence in the 3rd patient cleared at the end of 24 hours of streptomycin therapy. These results indicate the immediate beneficial effects on the acute toxic manifestations of the disease. This effect will probably

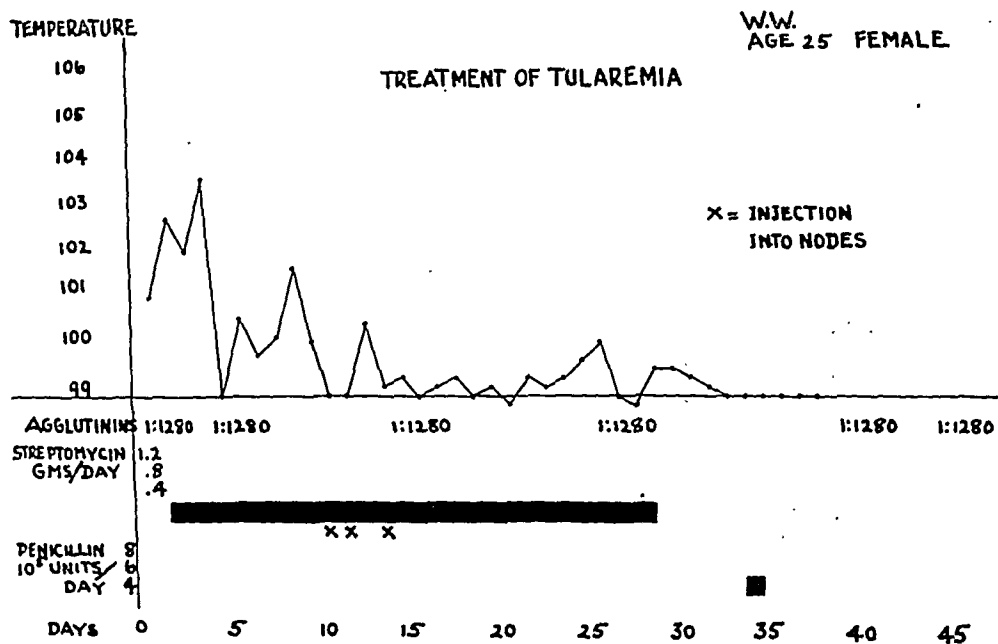


Fig. 5

tinued the same throughout her illness (Fig. 5). After 3 weeks of streptomycin therapy the patient developed symptoms of a threatening abortion, which failed to respond to obstetrical therapy. Examination of the fetus and placenta by the pathologist showed no pathologic changes which could be attributed to streptomycin or tularemia. Experience with this patient gave convincing evidence that local and systemic streptomycin therapy without surgical drainage was not the treatment of choice when tularemia lymphadenitis had reached the stage of suppuration.

**Discussion.** The beneficial effect of streptomycin was most striking in the 3

prove most valuable, since a good percentage of those patients who succumb to the disease do so in a severe state of toxicity by the end of the 2nd week.

Another feature which has shown a constantly favorable course has been the healing time of the primary lesion. In the 3 cases with primary lesions, healing was complete at the end of 10 to 15 days after streptomycin was started, in contrast to the usual average of 39 days.<sup>2</sup>

The response of the lymphadenopathy to streptomycin therapy was the most variable feature in this group of patients. In the 1st patient whose nodes were





## THE RÔLE OF THE LIVER IN RENAL SULFONAMIDE COMPLICATIONS

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THE rôle which the liver plays in renal sulfonamide complications is emphasized by the frequency of such developments in chronic hepatic diseases and in instances of sulfonamide hepatic injury. In a previous report<sup>21</sup> fourteen cases of renal sulfonamide complications were described and the hepato-renal relationship was referred to. Since that time 5 additional fatal sulfonamide complications have been studied making a total of nineteen. In this series of 19 cases there are 7 with marked hepatic morphologic change; 2 with portal cirrhosis, 1 with cholangitic abscesses, 1 with advanced fatty metamorphosis of the liver but with minor sulfonamide damage (not included in this report) and 3 which suffered serious liver change induced by the sulfonamide drug. These 7 cases represent only the non-obstructive renal complications which were directly or indirectly the cause of death; therefore, 37% of the cases studied have a background of liver damage either independent or the result of sulfonamide therapy. If 3 fatal obstructive cases are included with the above, the incidence is 53%; however, in the obstructive cases the morphologic changes in the liver were rather meager and therefore these are not included in the tabulations of this report even though there was some evidence of functional hepatic disturbance. Similarly minor morphologic alterations in the liver and kidney and clinical complications which were non-fatal are not included.

**SULFONAMIDE-LIVER RELATIONSHIP.**  
*Direct Sulfonamide Toxic Action on the Liver (Table 1).* Commonly reported clinico-pathologic findings of liver dis-

turbance during sulfonamide therapy include bilirubinemia, urobilinogenuria, decrease of prothrombin, depression of various liver function tests, alterations in serum colloidal gold reactions, enlargement of the liver and hemolytic anemia.<sup>1,12,14,24,28</sup> Morphologic changes frequently discussed are those of focal necrosis, fatty degeneration, coagulation necrosis and hepatitis.<sup>19</sup> The reports of human cases and the experimental data are quite similar; however, sulfanilamide, which is not important in the cause of hepatic damage in animals, is quite so in man.<sup>24</sup> Sulfathiazole is the most frequently encountered drug producing liver and renal complications. Next to it is sulfadiazine.

The liver which suffers from a chronic nutritional disease is more commonly injured by sulfonamide drug. There is general agreement in literature relative to portal cirrhosis, fatty degeneration, alcoholism and vitamin deficiencies.<sup>24</sup> Animal findings indicate the ease with which sulfonamides produce hepatic damage in experimental nutritional deficiency and the improvement of such cases with change in diet and supportive treatment with vitamin B, pantothenic acid, folic acid, biotin and liver extract.<sup>2,6,9,25,30</sup> It has been shown that sulfonamides interfere with the storage and utilization of the essential vitamins.<sup>4,22</sup> Such interference may, therefore, be of serious consequence in individuals partially depleted of these necessary metabolites. The same considerations apply in the discussion of other injurious agents in reference to the liver.<sup>11</sup>

The problem of individual tissue idio-

C O F	56	E. R. I., portal cirrhosis, diabetes	Sulfathiazole	128.4	1700 grams, granular, hard, tan  Fatty degener- ation of liver cells, portal cirrhosis, focal necrosis with eosino- phils, mono- cytes and poly- morphonuclears	100 grams, cortex 10 to 12 mm, loose capsule, speckled with hemorrhage, linear streaks, necrosis, pelvic hemorrhages  Granulomatous inflammatory reaction, vasculitis	Portal cirrhosis with allergic type of renal inflam- matory destructive reaction and vascu- litis. Uremia
A K M	68	Suppurative cholan- gitis, spon- taneous cholecysto- duodenos- tomy, chole- lithiasis	Sulfathiazole	270	2000 grams, many minute green-yellow abscesses  Central lobu- lar necrosis, old periportal fibrosis, cholan- gitic abscesses	350 grams, pale, granular  Granulomatous foci, plasma cells, lympho- cytes and eosino- phils, desquamated tubules, sulfic crystals in tubules	Chronic liver disease with cho- langitic abscesses. Development of uremia after sulfathiazole therapy. Nephrosis in chronic liver disease

rendered susceptible to the toxic actions of the drug resulting in various complications. This, of course, is particularly true in cases where there is a predisposing condition, such as chronic nutritional deficiency. Regardless of the mechanism, the state of liver injury with the added depression of the vital functions (detoxification) brought on by sulfonamide therapy immediately places an additional load upon the kidneys. The burden of detoxification, therefore, may be trans-

the circulatory disturbances of the individual organs. Lauck<sup>17</sup> has an excellent review and discussion of such occurrences under the title of "Lower Nephron Nephrosis."

*Sulfonamide Metabolism in the Liver* (Table 2). The liver metabolism of sulfonamide drugs has several points of consideration. The conjugation of sulfonamide drug with serum protein takes place apparently in the liver. Combination of the azo drug with protein serves as a

happen antigen; therefore, it becomes a problem of sensitization with repeated drug administrations. The lack of any correlation between the amount of drug used and the nature of the reaction suggests an allergic background. In many instances the history of previous sensitization is not obtained. This need not be alarming since the same situation may be encountered in serum sickness. The allergic or hypersensitivity phenomenon in reference to sulfonamide has been cited by

compared to the Arthus phenomenon. The close similarity of vascular changes induced by sulfonamide therapy and similar findings in serum sickness further emphasizes the hypersensitivity phenomenon.<sup>16</sup> The use of sulfonamides in small doses over long periods of time as prophylactic measures in certain diseases may yet be attended by sensitization complications to be noted in the future.

The other consideration of liver sulfonamide metabolism deals with nephrolith-

TABLE 2.—DATA OF CASES SHOWING CHANGES INCIDENT TO SULFONAMIDE METABOLISM IN LIVER

Name	Sex	Age	Clinical diagnosis	Drug used	Blood NPN	Liver	Kidney	Remarks
T P	F	30	Meningitis	Sulfadiazine	90	2230 grams, congested, swollen, speckled	650 grams, large, edematous bulging cut surfaces, pelvic hemorrhages, congested	Meningitis treated with sulfadiazine. Stopped and a few days later started again. Moderate morphologic hepatic changes but marked renal reaction with precipitation of crystals. Calcifications, nephrosis and hypersensitivity reaction
M B	F	31	U. R. I. dysuria	Sulfathiazole	150	Large, speckled	Interstitial inflammatory reaction eosinophilic, mononuclear and polymorphonuclear, tubular degeneration, small areas of interstitial and intratubular calcification. Few sulfacystals present	Prominent hepatic damage produced by sulfonamides complicated by anuria with marked tubular degeneration of the kidneys. Also vascular hypersensitivity reaction. Decapsulation done with promising result but death due to postoperative hemorrhage and uremia
M S	F	51	U. R. I.	Sulfathiazole and sulfadiazine	140	2300 grams, focal hemorrhagic spots	485 grams, large, loose capsule, mottled, pyramidal congestion, cortex speckled, pelvic hemorrhages	Sulfonamide focal necrosis of the liver complicated by severe tubular degeneration of the kidney and uremia. Hypersensitivity reaction
						Focal necrosis, eosinophilic and monocyctic portal infiltration	Marked tubular degeneration, crystals, eosinophilic cellular reaction around glomeruli, vasculitis	
						Focal cellular infiltration of polymorphonuclears, plasma cells and monocytes	590 grams, congestion, speckled surface, dull gray pyramids, pelvic hemorrhages	
							Tubular degeneration, debris in lumens, periglomerular cellular infiltration, perivascularitis	

Rich,<sup>26</sup> French,<sup>8</sup> Lichtenstein<sup>13</sup> and others. The frequent occurrence of rash and the recurrence of toxic manifestations upon repeated administrations of sulfonamide drugs would bear this out.<sup>15,20</sup> The tissues so sensitized include the kidneys, liver, skin and blood-vessels particularly. The reactions are similar to sensitization produced by foreign protein injections.<sup>15,26</sup> The morphologic changes in this respect are those of rather severe exudative inflammatory reactions that may well be

iasis. Although this report does not primarily deal with mechanical *obstructive* changes, it is necessary to mention the rôle which the liver plays in the production of sulfonamide crystals and sulfonamide protein combinations without directly clogging passages. The drugs undergo acetylation in the liver. This process apparently is not seriously influenced by hepatic disease. The degree of acetylation

and the distribution of the acetylated drug in the body varies with the different drugs. It is quite high in reference to sulfathiazole and is associated with a concentration of the drug in kidney tissue in excess of that found in the blood,<sup>2</sup> correlating the observations that sulfathiazole is the most serious of the drug in this respect. Likewise in states of dehydration there may be the problem of precipitation of the insoluble acetylated form. Adequate fluid administration has been cited as precluding the formation of mechanical renal complications.<sup>3</sup> Likewise the maintenance of an alkaline urine in which the sulfonamide conjugate products are more soluble prevents the occurrence of mechanical obstruction.<sup>15,21</sup> It has also been shown that sulfonamide compounds in the urine are more soluble in concentrated urine than they are in dilute<sup>2</sup> suggesting that renal disease associated with a low specific gravity may be the background for the development of mechanical obstruction. The artificial production of an increased specific gravity of the urine by the administration of urea has also been employed with satisfactory results.<sup>22</sup> In hepatic disease glucuronic acid production may be impaired, limiting conjugation of glucuronic acid and sulfonamides.<sup>27</sup> The glucuronic acid-sulfonamide combination is a soluble one and a high percentage of the drug may be excreted in this form; therefore, in conditions where this conjugation does not take place adequately a proportionate amount of the drug would be excreted as the less soluble acetylate form. The above points dealing with obstructive complications are equally applicable to the discussion of renal injury and inflammation produced by sulfonamide crystals in the absence of blockade.

**Summary.** The hepato-renal relationship in reference to sulfonamide renal com-

plications consists of: (a) Toxic injury to a previously diseased liver, (b) Hepatic protein-sulfonamide metabolism leading to formation of hapten antigen, (c) Injury on the basis of hypersensitivity reactions, (d) Formation of relatively insoluble acetyl-sulfonamide compounds which lead to mechanical obstruction or irritation resulting in inflammation and (e) impairment of glucuronic acid-sulfonamide conjugation (soluble) accentuating item (d).

**Conclusions.** 1. The incidence of hepatic disease as a background in renal sulfonamide complications is emphasized by the presence of liver damage in 6 cases (37.5%) of the fatal non-obstructive sulfonamide nephrosis. Lesser hepatic lesions were found in 4 additional cases, 3 of them with sulfonamide lithiasis, making a total of 10 cases (53%).

2. Morphologic hepatic lesions readily distinguishable from the primary disease were the only criteria used in reporting these cases; the remaining cases of sulfonamide kidney damage are excluded because outstanding morphologic changes were absent and functional studies of the liver incomplete or lacking.

3. The specific nature of the hepatic lesion is not as important as the fact of diffuse liver impairment and is not correlated with the seriousness of renal injury.

4. Liver diseases of nutritional deficiencies (notably portal cirrhosis) increase the likelihood of renal complications from sulfonamide therapy. Likewise, renal complications are more frequent when the liver is injured by the administered sulfonamide.

5. Such findings should caution against the unwarranted administration of sulfonamide drugs to patients with chronic hepatic disorders and to those manifesting hypersensitivity phenomena.

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## TOLERANCE TO INTRAVENOUSLY ADMINISTERED PROTEIN HYDROLYSATE IN SEVERE HUMAN LIVER CIRRHOSIS\*

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IN the treatment of human liver disease, particularly cirrhosis, a high protein diet has been shown to be of therapeutic value.<sup>1,2,3,4,5,6</sup> Protein hydrolysates have been given intravenously to ill patients to replace or supplement the protein which the patient was able to take by mouth. The question has arisen whether or not such hydrolyzed proteins or amino acid solutions are normally utilized in an individual with a damaged liver. It may be argued that such patients may fail to deaminate the injected amino acids as rapidly as normal individuals or fail to synthesize tissue protein.

Kitamura,<sup>7</sup> using injections of single amino acids, found in the normal rabbit that the plasma  $\alpha$ -amino nitrogen level returned to its original level 30 to 60 minutes after injection, but in rabbits whose liver had been damaged by carbon tetrachloride or chloroform, the amino nitrogen level was still elevated 24 hours after the injection. Mann and Bollman<sup>12</sup> found in dogs deprived of most of their hepatic tissue that intravenous amino acids gave only slight elevation of the blood amino acid concentration and suggested that most of the excess was adsorbed into the tissues.

Goettsch and Lyttle<sup>11</sup> found retention of amino acids after the administration of

"amigen" to children with liver disease and to hypoproteinemic dogs. The retention in the latter, they suggested, was due to impaired liver function. Stewart and Rourke<sup>17</sup> in contrast found no differences in plasma amino acid concentrations or amino acid excretions, between patients with and without liver disease after the administration of "amigen." Bernhart and Schneider<sup>1</sup> found a diminished tolerance to the administration of 4 gm. of tyroxine in the presence of liver disease.

Fagin and Zinn<sup>2</sup> treated a group of 5 patients suffering from cirrhosis for 1 month with daily injections of 300 cc. of 15% protein hydrolysate solution, and noted decrease in both liver size and in the peripheral edema. They did not study blood or urine amino acid concentration.

It might be expected that if the cirrhotic liver failed to metabolize injected amino acids properly, one would find an increase in the amino acid concentration of the blood or a prolonged amino acidemia. A reduced rate of urea formation might also be expected, resulting in a lower blood urea concentration than would be encountered in normal individuals. The present investigations were designed to compare the amino acid metabolism in normal individuals and in patients with cirrhosis of the liver, by measuring the rate of

\* The expenses of this investigation were defrayed in part by a grant from the Abbott Laboratories, North Chicago, Illinois, to Harvard University.

$\alpha$ -amino nitrogen removal from the peripheral blood and the rate and duration of the rise in urea nitrogen in a series of normal subjects and in patients suffering from severe liver disease. Additional studies were made of the nitrogen partition of the urine of these 2 groups of individuals. Furthermore, in order to put the greatest possible load on the liver of the subjects studied, the hydrolysate given was administered as rapidly as possible and in as large doses as possible.

**CLINICAL MATERIAL.** The eight patients suffering from severe liver disease were chosen for study from the wards of the Boston City Hospital. The clinical diagnosis of all 8 of these patients was Laennec's cirrhosis. Seven of the 8 patients gave a history of long-standing alcoholism and all of them had consumed diets low in protein and the B complex. Table 1 shows the clinical and laboratory data on which these diagnoses were based. Subsequently, all of these patients died of their disease or associated disturbances and anatomic diagnoses are given whenever possible.

As normal controls, 5 well-nourished hospital patients without evidence of liver disease were studied. The diagnoses in these cases were: primary syphilis, 2; renal colic, 1; old cerebrovascular accident, 1; convalescent rheumatic fever, 1. Treatment had been completed on these patients and they were ready for discharge at the time of study.

Table 2 shows the laboratory findings in these 5 "normal" patients. None of these patients had an enlarged liver, palpable spleen, ascites, edema, spider angiomas or jaundice.

**Material and Methods.** The test dose of amino acids consisted of 300 cc. of a 15% acid hydrolysate of casein\* fortified with tryptophane, diluted to 500 cc. with 0.85% sodium chloride solution. This material on analysis in our laboratory was found to contain 2.1 gm. of nitrogen in 100 cc., of which about 75% was  $\alpha$ -amino nitrogen or 4.7 gm. of  $\alpha$ -amino nitrogen in the amount used.

The test dose was injected intravenously, usually in exactly 1 hour, to the fasting subjects. Occasionally, due to distressing symptoms, it was necessary to take a few minutes longer for the injection.

In the first few tests made, blood samples were taken prior to the injection, when half the amino acids had been administered, at the end of the injection, and 1 and 4 hours thereafter, and were analyzed for content of non-protein nitrogen, urea nitrogen and  $\alpha$ -amino nitrogen. It was soon found that the determinations during and at the end of the injection period were directly dependent on the rate of infusion, and these were discontinued. In the later tests, blood samples were collected before, and 1 hour and 4 hours after the infusion. Separate samples of urine were obtained when possible at the end of the infusion period, 4 hours following the infusion and then for the following 19 hours; and were analyzed separately for the total content of nitrogen, urea nitrogen and  $\alpha$ -amino nitrogen.

On the initial blood of each patient the following additional determinations were performed—total protein and albumin globulin fractionation,<sup>8</sup> prothrombin time,<sup>15</sup> serum bilirubin,<sup>12</sup> complete blood count and cephalin-cholesterol flocculation.<sup>6</sup> During the 1st few days after admission, a determination was made of the percentage of bromsulfalein excreted 45 minutes after the administration of 5 mg. per kilogram of body weight.

The  $\alpha$ -amino nitrogen was determined by the gasometric ninhydrin carbon dioxide method of Van Slyke;<sup>5,18</sup> non-protein nitrogen by Folin's micro-Kjeldahl method with direct nesslerization,<sup>4</sup> urea nitrogen by the urease method of Folin<sup>7</sup> with distillation and nesslerization. Albumin globulin separation was made by the Howe method<sup>8</sup> and albumin and total plasma proteins were determined by modification of the micro-Kjeldahl method of Keys.<sup>8</sup>

**Results.** Table 3 shows the blood biochemical findings in both the normal subjects and patients with cirrhosis. The mean normal fasting value for plasma  $\alpha$ -amino nitrogen in this laboratory is 3.73 mg. per 100 cc., with a standard deviation of 0.29, giving a "normal" range of 2.86 to 4.60 mg. per 100 cc., using 3 times

\* Parenamine—supplied through the kindness of Frederick Stearns Co., Detroit, Mich.



TABLE 1.—CLINICAL AND LABORATORY OBSERVATIONS IN PATIENTS WITH CIRRHOSIS OF THE LIVER

Patient, age and sex	Alcoholic history*	Diet (fair or poor)	Duration from first symptom	Ascites*	Edema*	Liver size (cm.)	Distended abdominal veins	Spider angiomas	Visible jaundice	Thrombocytopenia†	Cephalic rhinorrhea†	Serum bilirubin (mg./100 cc.)	Plasma protein (gm./100 cc.)	Prothrombin time (sec.)	Time of death (days)
E. B., 45 F	4+	4+	1 yr.	4+	1+	3	++	0	0	+	+	1.40	2.3	15	11
J. S., 63 M	4+	4+	6 wks.	3+	2+	3	++	0	0	+	+	3.40	2.5	15	11
R. M., 48 M	2+	4+		4+	4+	N.P.†	++	0	0	40	+	0.78	2.2	12	14
E. M., 42 M	4+	4+	8 "	4+	1+	10	++	0	+	52	+	6.50	1.4	11	12
T. McC., 70 F	0	4+	2 yrs.	4+	3+	N.P.†	++	+	0	32	3+	1.20	2.1	15	13
C. S., 40 M	4+	4+	8 mos.	2+	2+	1	++	+	0	40	+	0.20	2.6	15	13
E. C., 39 F	4+	4+	15 yrs.	4+	4+	4	++	+	+		+	4.20	2.1	17	10
P. D., 70 M	4+	4+	10 "	4+	4+	N.P.†	++	0	+		+	1.70	1.5	15	15

\* 0 to 4+.

† % retention 45 minutes after administration of 5 mg. per kilo body weight.

‡ Not palpable.

TABLE 2.—LABORATORY OBSERVATIONS IN THE PATIENTS WITHOUT LIVER DISEASE

Patient, age, sex	Serum bilirubin (mg./100 cc.)	Plasma protein (gm./100 cc.)	Prothrombin time (sec.)
C. D., 42 M	Total 0.72	Albumin 4.4	12
J. F., 70 M	direct 0.60	4.1	12
L. F., 29 M	0.22	3.7	11
L. D., 29 M	0.18	3.0	14
C. A., 41 M	0.01	4.1	13
G. A., 41 M	0.18	3.8	20
A. M., 65 F	0.10	3.1	20
	0.66	2.9	21

the standard deviation to minimize variation due to chance alone. In the subjects studied the fasting or initial  $\alpha$ -amino nitrogen level was within the normal range with one exception. This exception was a patient with cirrhosis whose initial

the cirrhotic group being slightly higher than that of the normal group. By 4 hours after the infusion the mean value for the normal group was within the normal range but still slightly above the pre-infusion levels. Only 2 of the cirrhotic

TABLE 3.—CHANGES IN PLASMA NON-PROTEIN, UREA AND  $\alpha$ -AMINO NITROGEN FOLLOWING INTRAVENOUS INJECTION OF 300 CC. 15% PROTEIN HYDROLYSATE SOLUTION

atient	Non-protein nitrogen (mg./100 cc.)			Urea nitrogen (mg./100 cc.)			$\alpha$ -Amino nitrogen (mg./100 cc.)		
	Before injection	After injection		Before injection	After injection		Before injection	After injection	
		1 hr.	4 hr.		1 hr.	4 hr.		1 hr.	4 hr.
CIRRHOSIS									
E.B.	18.1	25.2	20.0	9.5	11.4	13.0	3.59	11.85	5.51
J. S.	34.0	38.4	37.2	18.0	17.9	19.0	4.10	7.41	6.16
R. M.	20.2	25.5	22.4	9.0	11.9	17.2	4.26	6.52	6.10
F. M.	20.0	30.8	22.4	8.6	9.1	13.1	2.68	6.51	3.39
T. McC.	41.2	46.8	42.4	25.7	28.4	29.3	3.78	7.70	5.15
E. C.	18.1	19.4	18.6	10.8	9.7	7.9	3.61	7.71	6.00
P. D.	27.6	36.0	29.2	16.4	19.5	19.7	4.21	12.61	8.18
C. S.	30.4	32.8	30.0	15.0	16.3	16.3	3.64	6.31	3.77
Mean	26.2	31.9	28.5	14.1	15.5	16.9	3.73	8.33	5.53
NORMAL									
C. D.	27.0	35.0	38.2	11.7	14.3	18.5	3.45	9.58	4.22
J. F.	23.6	30.8	25.1	13.0	15.7	15.8	4.52	7.21	4.57
I. D.	20.8	26.0	27.2	10.5	14.3	15.2	4.09	4.99	4.27
G. A.	27.6	33.6	26.0	13.4	19.1	17.4	3.64	7.12	4.90
A. M.	21.7	25.3	23.1	9.5	13.2	13.6	4.13	8.66	4.44
Mean	24.1	30.1	27.9	11.6	15.3	16.1	3.97	7.51	4.48

TABLE 4.—CHANGES IN URINE TOTAL, UREA AND  $\alpha$ -AMINO NITROGEN FOLLOWING INTRAVENOUS INJECTION OF 300 CC. OF 15% PROTEIN HYDROLYSATE SOLUTION

Patient	Total nitrogen (gm.)			Urea nitrogen (gm.)			$\alpha$ -Amino nitrogen (gm.)			% of injected $\alpha$ -amino nitrogen excreted during and 4 hrs. after infusion
	During infusion	During 4 hrs. after infusion	During following 19 hours	During infusion	During 4 hrs. after infusion	During following 19 hours	During infusion	During 4 hrs. after infusion	During following 19 hours	
CIRRHOSIS										
R. M.	1.52	1.93	9.60	0.92	1.29	7.20	0.230	0.190	0.190	9.0
T. McC.	..	1.46*	6.35	..	1.08*	4.50	..	0.066*	0.121	1.4
E. C.	0.48	0.77	4.02	0.27	0.57	3.50	0.106	0.138	0.092	5.2
P. D.	0.95	..	..	0.54	..	..	0.166	..	..	..
C. S.	1.30	2.23	..	0.84	1.20	..	0.067	0.100	..	3.6
NORMAL										
C. D.	0.97	0.83	..	0.54	0.54	..	0.172	0.104	..	5.9
J. F.	0.60	3.53	7.81	0.32	2.10	5.47	0.043	0.268	0.097	6.6
I. D.	4.95	4.04	8.36	4.15	2.77	5.33	0.222	0.085	0.116	6.6
G. A.	1.00	0.64	8.32	0.82	0.43	6.63	0.014	0.010	0.437	0.5
A. M.	0.44	2.01	5.00	0.38	1.28	3.20	0.048	0.025	0.013	1.6

\* Pooled specimens during infusion and 4 hours after infusion.

level was slightly below normal. In the few analyses made during and at the end of the infusion, the  $\alpha$ -amino nitrogen values varied from 10 to 13 mg. per 100 cc. of plasma. One hour after completion of the infusion all of the plasma  $\alpha$ -amino nitrogen values were elevated, the mean of

group had returned to normal. The mean value for the cirrhotic group was 5.53 mg. per 100 cc. which is significantly above our normal range.

The data in Table 3 show that the plasma urea nitrogen in most instances, in both the "normal" controls and the

cirrhotic patients, rose slightly, reaching the highest observed levels 4 hours after the infusion.

Analyses for total nitrogen, urea nitrogen and  $\alpha$ -amino nitrogen were made in urine samples, and the results are presented in Table 4. In several instances in which it was impossible to be sure of complete collections the data has not been presented so that the data on only 5 of the cirrhotic patients are included. The variation between individuals is so large that no significant difference in excretion of either urea or  $\alpha$ -amino nitrogen was observed between the normal individuals and patients with cirrhosis following the injection of 4.66 gm. of  $\alpha$ -amino nitrogen.

A few patients complained of a burning sensation and flushing early in the infusion, but this did not last for more than a few minutes. Nausea and vomiting were frequent late in the infusion and could be stopped by slowing or momentarily stopping the injection. In 2 patients it was observed that these symptoms developed when the infusion was run in more rapidly than 8 cc. or 9 mg. of nitrogen per minute. Incidentally it was noted that patients who had recently received heavy sedation showed less nausea and vomiting.

**Discussion.** The object of these investigations was to determine tolerance to, and, if possible, the fate of injected amino acids in patients suffering from severe liver disease. Clinically, there was no difference in tolerance for injected amino acid between the normal and cirrhotic groups.

Biochemically the data indicate that probably there was a slower rise of the mean plasma urea concentration and possibly a slightly elevated mean plasma  $\alpha$ -amino nitrogen level 4 hours after the infusion of the protein hydrolysate in the cirrhotic group as compared to the normal. However, there is considerable individual variation in the cirrhotic group and 2 of the patients showed as marked a rate of urea formation as obtained in the normal controls. There is no evidence that amino acids are not metabolized by the

cirrhotic individual as well as by the normal individual in the amount and at the rate which were used in this presentation. The only safe conclusion from this study may lie in the statement that there is possibly a slight diminution in the rate of amino acid disappearance from the circulating blood and slight decrease in urea formation.

The experiments of Kitamura *et al.*<sup>9</sup> cannot be compared with the results in our cases since the damage done to the liver by chloroform in rabbits is probably, so far as biochemical studies indicate, much more severe than in cirrhosis. Previous attempts to use orally administered protein and its hydrolytic products in man as a means of measuring liver function by increased accumulation of unmetabolized  $\alpha$ -amino nitrogen in the plasma, or by decreased urea formation, have not met with success. In the small series of cases reported here, the intravenous administration of 4.66 gm. of  $\alpha$ -amino nitrogen does not indicate any marked impairment of the cirrhotic liver to metabolize  $\alpha$ -amino nitrogen, as demonstrated by the same criteria as used for the oral liver function tests mentioned previously. The present studies do indicate the necessity for further study of this problem using either mixtures of synthetic amino acids or suitable hydrolysates which may be administered in much larger amounts and in shorter periods of time.

Incidentally, it was learned that in the normal patient approximately 5 hours are needed to remove from the blood the excess  $\alpha$ -amino nitrogen added by the injection of protein hydrolysate containing 4.66 gm. of  $\alpha$ -amino nitrogen.

**Conclusions.** 1. Three hundred cc. of 15% protein hydrolysate containing 75% of  $\alpha$ -amino nitrogen was given by rapid intravenous infusion to 8 patients with cirrhosis of the liver and to 5 "normal" patients.

2. Clinically both groups showed some intolerance to the rapid infusion, exhibiting flushing, nausea or vomiting.

3. Plasma non-protein, urea and  $\alpha$ -amino nitrogen were determined initially and 1 and 4 hours after the infusion. All patients showed elevation of the  $\alpha$ -amino nitrogen values 1 hour after the infusion but by 4 hours after the infusion the group without liver disease had returned to normal levels in contrast to the group with cirrhosis of the liver which still exhibited some elevation in the  $\alpha$ -amino nitrogen values. The urea nitrogen, while subject to great individual variations, rose more slowly and to a lesser degree in the cirrhotic group. There is, therefore, a pos-

sibility that there is a slight reduction in the rate of metabolism of the amino acid administered.

4. Few important data were obtained from biochemical studies of the urine, except to demonstrate that relatively small amounts of  $\alpha$ -amino nitrogen are excreted following rapid injection of the material.

5. In the amounts used and at the rate administered in this study, the injection of amino acids does not offer a good method of determining liver impairment even in the presence of advanced liver cirrhosis.

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## URINARY EXCRETION OF 3,3-DIETHYL-2,4-DIOXOTETRAHYDROPYRIDINE IN MAN

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STUDIES of the urinary elimination of 3,3-diethyl-2,4-dioxotetrahydropyridine, a sedative-hypnotic, have been carried out in dogs,<sup>2,4</sup> cats, rabbits and mice<sup>3</sup> by other investigators. Following the recent development of a new fluorometric method for the determination of the drug in urine,<sup>2</sup> a study of the renal excretion in man was undertaken as a collateral project of the clinical evaluation of the drug in psychiatric conditions.<sup>6</sup> The object of the present investigation was to obtain information on the excretion of 3,3-diethyl-2,4-dioxotetrahydropyridine, during and after a prolonged course of daily medication, as compared with the elimination following a single dose.

**Case Material and Procedure.** Ten psychiatric cases, five males and five females, ranging in age from 20 to 41 years, were studied. These patients, who did not require sedative-hypnotic medication, were to have received 0.6 gm. of the drug† every night for a period of four weeks. However, medication had to be omitted on some days in several instances, and in one uncoöperative patient (Case No. 109), it became necessary to discontinue the administration of the drug after

two weeks. Had the patients received medication according to plan, the total intake of each person would have been 16.8 gm. Table 1 shows the quantities actually ingested.

TABLE 1.—TOTAL DOSE OF NU 903 INGESTED BY TEN PSYCHIATRIC PATIENTS WITHIN 28 DAYS.

Case No.	Total dose administered, gm.
101	15.6
102	16.8
103	16.8
104	13.2
105	16.8
106	12.6
107	13.2
108	16.8
109	6.0
110	16.8

In order to determine the amounts of NU-903 excreted, daily collection of 24-hour urine specimens was instituted 1-13 days after the initial dose. However, in the majority of cases some voidings had to be discarded because of incompleteness of collection, and the study of the urines of patient No. 105 was abandoned altogether when it became obvious that she could not be trained to collect her specimens. In the remaining 9 patients collection was continued for

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† Hoffmann-La Roche, Inc., of Nutley, N. J., supplied 3,3-diethyl-2,4-dioxotetrahydropyridine in form of tablets of 0.2 gm. under the designation of NU-903. 0.2-0.4 gm. having been found to be effective in inducing sleep in cases of mild and medium insomnia, the daily amounts administered to the 10 subjects reported here are in excess of the average adult dose.

at least 4 days after the last dose of NU-903.

Amber bottles, containing 20 ml. of 3.5N  $\text{H}_2\text{SO}_4$  were used for pooling the daily voidings of each subject. In carrying out the estimations of the urinary excretion of NU-903 in all the specimens thus obtained, the method described by Hirschberg *et al.*<sup>2</sup> was used. This technique is based on the measurement of the comparative fluorescence of urines, at suitable dilutions, in the absence and presence of hydroxylamine. The difference in intensity between total fluorescence (without hydroxylamine treatment) and residual fluorescence (with hydroxylamine treatment) yields a measure of the concentration of NU-903 in urine.

from 24.2–64 mg. It can be furthermore seen from the same table that by expressing the average amounts of NU-903 excreted in mg./1000 ml. urine, rather than in mg./day, this range is restricted to from 24.7–38.4 mg. Thus the average amounts of the drug excreted per 1000 ml. urine by the individual subjects are in closer agreement than those calculated on a per diem basis. Similarly, the standard deviations are significantly smaller when all values are calculated on the basis of mg./1000 ml. It seems as though the average amount of NU-903 excreted is related to some extent to the average volume of the voidings.

Figure 1 portrays the experimental procedure and the results obtained in case

TABLE 2.—URINARY EXCRETION OF NU-903 FOR 9 PSYCHIATRIC PATIENTS DURING PROLONGED COURSE OF MEDICATION (0.6 GM. PER DOSE; RANGE OF TOTAL INTAKE 6–16.8 GM.).

Case No.	No. of urine specimens	Average excretion of NU-903 in mg./day	Average volume of urine in ml./day	Average excretion of NU-903 in mg./1000 ml.
101	19	54.0 $\pm$ S.D. 26.4	1460	37.2 $\pm$ S.D. 8.4
102	21	37.4 $\pm$ S.D. 12.5	1200	31.4 $\pm$ S.D. 7.4
103	15	24.9 $\pm$ S.D. 13.6	640	38.4 $\pm$ S.D. 9.6
104	8	46.2 $\pm$ S.D. 7.4	1320	35.4 $\pm$ S.D. 6.8
106	8	43.4 $\pm$ S.D. 8.2	1300	35.0 $\pm$ S.D. 7.8
107	9	24.2 $\pm$ S.D. 11.9	810	29.0 $\pm$ S.D. 7.3
108	11	29.8 $\pm$ S.D. 13.1	800	36.6 $\pm$ S.D. 8.4
109	8	64.0 $\pm$ S.D. 15.6	1700	38.1 $\pm$ S.D. 6.5
110	11	31.1 $\pm$ S.D. 19.9	1210	24.7 $\pm$ S.D. 11.6
Mean value	12.2	39.4 $\pm$ S.D. 14.3	1160	34.0 $\pm$ S.D. 8.2

After a rest period of two months without medication, a single dose of 0.6 gm. of NU-903 was administered to 6 of the 10 subjects (Case Nos. 101, 102, 104, 106, 108 and 109). Again 24-hour urine specimens were collected for 4 days after the intake of the drug and the excretion values of NU-903 determined. In addition, a similar number of urine specimens were assayed of two normal, self-controlled persons (chemists) who had taken a single dose of 0.6 gm. of the drug.

**Findings and Interpretation.** *Excretion of NU-903 during and after a prolonged course of daily medication.* As appears from Table 2, the average amounts of NU-903 excreted per day by the individual patients receiving a daily dose of 0.6 gm. over a prolonged period of time ranged

No. 102. This particular patient was chosen for the graphical presentation of the representative findings because she was distinguished by excellent coöperation: Thus never during the 4-week period of daily administration of NU-903 did she omit taking a dose; moreover, she furnished the greatest number of urine specimens obtained from any of the subjects.

As can be seen from Figure 1, the daily excretion values of NU-903 varied considerably, ranging in this case from 17.6–69.2 mg. The validity of the inference, drawn from the composite Table 2, namely that the average amount of NU-903 excreted by a given person is related to the average volume of the voidings, is borne out by the daily excretion findings for patient No. 102. The peak of elimina-

tion occurring on the 18th day of the experiment coincides with the largest volume (1730 ml.) of any of the 24-hour urine specimens of this patient. On the other hand, the minimum amount of NU-903 excreted is correlated with a urinary volume (730 ml.) which is second to the smallest collected by her in any 24-hour period. Of particular interest are the excretion findings on the days following the last dose of NU-903, *i. e.*, in case No. 102 after a total intake of 16.8 gm. As appears from Figure 1, the excretion level decreased promptly following discontinuation of the drug and after 3-4 days only negligible quantities of NU-903, if any, were detectable in the urine. The pertinent findings in the other 8 cases were quite similar, as evidenced by the figures recorded for 5 of these, together with the data for case No. 102, in the left hand section of Table 3.

range from 33-73 mg. (5.5-12.7% of the single dose). Furthermore, it appears that the mean total excretion of these 6 patients is 61 mg. (10% of the single dose) and that the mean value of excretion on the first day (33 mg.) amounts to 55% of the mean value of the total quantities eliminated. The mean values of the amounts excreted during the second, third and fourth 24-hour period of collection represent 26, 11, and 8% respectively of the total excretion. In general, this pattern of elimination resembles that after the prolonged course, but the mean total excretion after the terminal dose of the latter is somewhat higher, namely 76 mg. Interestingly enough the mean values of excretion on the respective second, third, and fourth days after the prolonged course on the one hand and following the single dose on the other, are almost identical, with the higher excretion value on the first

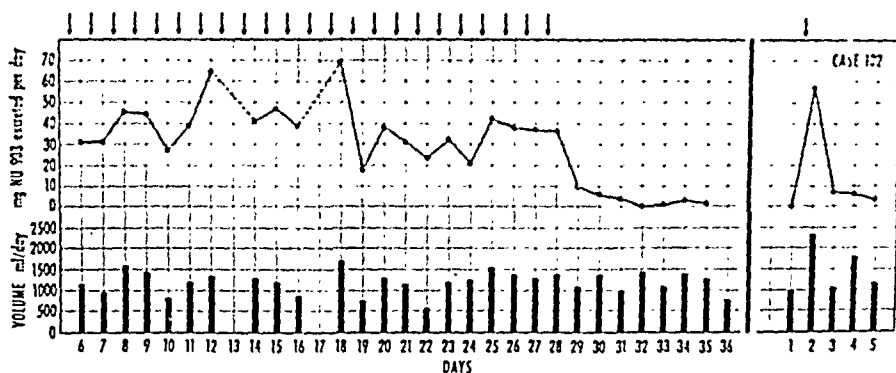


FIG. 1.—Urinary excretion of NU-903 for patient No. 102 receiving a daily dose of 0.6 gm. for 28 consecutive days and, after a rest period of two months, a single dose of 0.6 gm. The initial estimation of NU-903 was performed after patient had taken six doses and with the exception of two days, indicated by broken lines, urinary assays were carried out daily until 8 days following discontinuation of medication. The excretion findings after the single dose are given to the right of the dividing line. The arrows represent the daily doses of NU-903.

*Excretion of NU-903 Following a Single Dose.* The excretion data of the 6 patients receiving a single dose of 0.6 gm. following a medication-free interval of 2 months, are recorded in Table 3, to the right of the dividing line. It can be seen that the quantities of NU-903 excreted by the individual subjects on the first day range from 15-57 mg. (2.5-9.5% of the single dose) and that their total excretion values

day accounting for the greater total elimination after the 28-day course. Undoubtedly, the amounts excreted by the individual patients during these first 24 hours are composed of a major portion originating from the last dose and a smaller portion from the preceding one. Obviously, there can be no such additive excretion after a single dose. Notwithstanding the somewhat higher excretion follow-

ing the prolonged administration, these findings indicate that no accumulation of the drug occurs even if given daily in comparatively large doses over a period of 4 weeks. This is entirely in keeping with the clinical results<sup>6</sup> which are characterized by a negligible percentage of after-effects. Particularly the absence of hang-

voidings on the first day contained the greatest portions of the drug excreted over a 4-day period. The total quantities of NU-903 eliminated were 31 mg. and 39.1 mg. (5.2% and 6.5% of the dose given). These values are in agreement with the lowest of the excretion figures recorded for the psychiatric patients. In general the

TABLE 3.—URINARY EXCRETION OF NU-903 FOR SIX PSYCHIATRIC PATIENTS AFTER LAST DOSE OF PROLONGED COURSE OF MEDICATION (0.6 GM. PER DOSE; RANGE OF TOTAL INTAKE 6-16.8 GM.) AND AFTER SINGLE DOSE OF 0.6 GM.

(Brackets indicate that total excretion values include individual findings of first, second, and fourth days only because of incompleteness of specimens collected on third day. Note close agreement between mean value of excretion on first day following last dose of prolonged course and mean value of composite average excretions per day during prolonged course.)

Case No.	Average excretion of NU-903 in mg./day during prolonged course	Excretion of NU-903 in mg. after last dose of prolonged course					Excretion of NU-903 in mg. after single dose				
		1st day	2d day	3d day	4th day	Total	1st day	2d day	3d day	4th day	Total
101 . . .	54	49	36	11	5	101	27	20	5	9	61
102 . . .	37	36	10	6	4	56	57	7	6	3	73
104 . . .	46	50	11	4	3	68	15	11	4	3	33
106 . . .	43	42	11	..	3	(56)	33	19	6	5	63
108 . . .	30	36	16	9	5	66	31	15	10	6	62
109 . . .	64	86	20	..	4	(110)	33	25	10	8	76
Mean value .	46	50	17	8	4	76	33	16	7	5	61

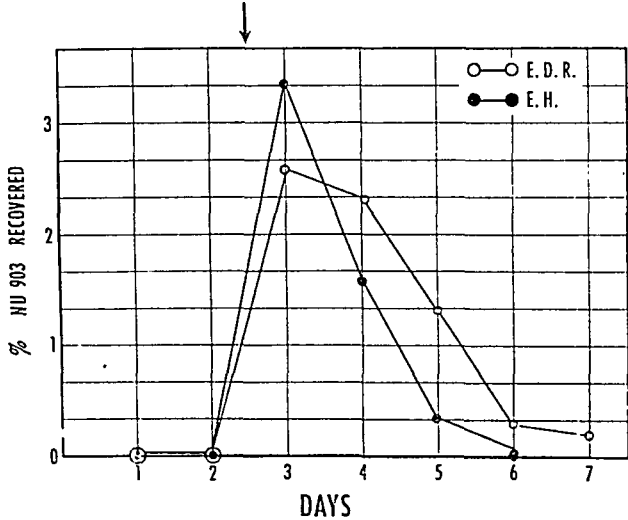


FIG. 2.—Urinary excretion of NU-903 for two normal adults receiving each a single dose of 0.6 gm. Estimations were carried out on two days prior to the administration of the drug (indicated by arrow) and four and five days respectively thereafter.

over and drowsiness on awakening, so frequently encountered with other hypnotics, may be explained by the rapid elimination of NU-903 and by the fact that no accumulation occurs. Figure 2 indicates the daily urinary excretion findings for the two normal self-controlled adults who took a single dose of 0.6 gm. of NU-903. As can be seen, the

course of excretion after a single dose was the same in all the eight subjects studied. An excretion of only 5.2-12.7% is suggestive of the possibility that a portion of the ingested dose is excreted in some conjugated form<sup>1</sup> not susceptible to direct assay. However, attempts to increase the amount of fluorescent material by acid or alkaline hydrolysis were unsuccessful.



Unpublished experiments conducted in these laboratories and elsewhere<sup>3</sup> have shown that NU-903 is fairly susceptible to alkaline oxidation resulting in breaking of the pyridine ring. It is probable that the major portion of the drug undergoes oxidation *in vivo*.

**Summary.** The urinary excretion of 3,3-diethyl-2,4-dioxotetrahydropyridine, a sedative-hypnotic designated NU-903, was studied in 9 psychiatric patients during and after a prolonged course of medication (0.6 gm. per dose with the total intake ranging from 6-16.8 gm.) and in 6 of these following a single dose of 0.6 gm. In addition the renal elimination of the drug was studied in two normal adults after the intake of 0.6 gm.

The average amounts of NU-903 excreted per day during the prolonged course were found to vary greatly from patient to patient and in a given subject the quantities eliminated within 24 hours varied from day to day. If the renal excretion was expressed in mg./1000 ml., these differences were rendered appreciably smaller. It appears that the quantities of NU-903 eliminated are related to the volume of the voidings. The mean value of the average daily

excretions during the continued administration was 6.6% of the individual dose.

Daily excretion studies after the last dose of the prolonged course showed that the level of elimination decreased rapidly following discontinuation of the drug. The mean value of the total amounts excreted by six patients on the four days after the last dose was 76 mg. More than 65% of this amount was eliminated on the first day.

The results following a single dose of 0.6 gm. were quite similar. Under these experimental conditions too, the excretion level dropped promptly and the mean value of the total amounts eliminated over four days was 61 mg. The excretion data in the two normal adults resembled those in the psychiatric patients. The rate of elimination in the 8 subjects receiving a single dose of 0.6 gm. ranged from 5.2-12.7% of the ingested amount.

The somewhat greater total excretion of NU-903 after the last dose of the prolonged course is due to a higher urinary level on the first day after cessation of medication. The findings indicate that no accumulation of the drug occurs even if it is given in large doses over a period of four weeks.

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## GASTRIC SECRETORY RESPONSE IN HYPOGLYCEMIA AS PRODUCED DURING INSULIN SHOCK THERAPY

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THE purpose of this report is to emphasize that insulin shock therapy as employed in the treatment of mental disease may cause serious side effects. This study, made at the Western Pennsylvania State Psychiatric Institute, reveals the increase in gastric acidity in patients with schizophrenia when given insulin shock therapy.

**REVIEW OF LITERATURE.** Gastric secretions are known to be modified by reflex nervous stimuli. By feeding dogs through gastric fistulae, the gastric secretions are smaller in volume and are of lower acid and peptic power than when food is fed by mouth (Babkin<sup>1</sup>). When the gustatory nerves are stimulated, reflexes are mediated *via* the vagus nerves to the stomach to cause a secretory response. Pavlov (cited by Babkin<sup>2</sup>) showed that following double vagotomies in dogs sham feedings produced only a small volume of neutral or slightly acid mucus with no peptic power. Thornton, Storer and Dragstedt<sup>18</sup> reported the same findings in man. Ten patients given sham feedings showed an increase in both the volume and acidity of the gastric secretions. After bilateral vagotomies in these patients no secretory response was noted.

The positive influence of the vagus nerves upon the stomach was well shown by Vineberg<sup>3</sup> working in Babkin's laboratory. By exposing the vagi in the neck of a dog and stimulating them directly with electrical currents, he showed that weak stimuli produced an alkaline or slightly acid gastric secretion, while strong stimuli produced a large volume of highly acid juice with strong digestive power. Stimulation of the vagi by means of drugs

will produce the same results. Flexner and Wright<sup>10</sup> used acetyl-beta-methylcholine (Mecholyl), a parasympathomimetic drug, and found that an increase in gastric acidity resulted. The effects of indirect vagal stimulation through the parasympathetic center in the brain have been proven. Hypoglycemia in dogs following administration of large doses of insulin causes a marked increase in volume, acidity and digestive power of their gastric juice (LaBarre and de Cespedes,<sup>13</sup> Babkin<sup>5</sup>). Reestablishment of normal blood sugar levels in these dogs will result in a return of the gastric secretions to normal values (LaBarre and de Cespedes<sup>15</sup>).

The relative ease of the production of insulin hypoglycemia and the constancy of its action in the stomach has prompted Babkin<sup>6</sup> to recommend the use of insulin as a test of the functional ability of the gastric mucosa. This same property of insulin is made use of following gastric neurectomies (vagotomies) in the treatment of peptic ulcer in man. If, after operation, large doses of insulin fail to cause an increase in the gastric acidity, it is considered that all the nerve fibers have been severed (Thornton, Storer and Dragstedt<sup>18</sup>). Vanzant<sup>19</sup> reported a 2½ year follow-up on 4 dogs after vagotomy and, by the renewed gastric response to insulin hypoglycemia, concluded that the vagus nerves were again transmitting impulses to the stomach.

The effect of the vagi upon the stomach can be effectively eliminated by physiologic doses of atropine. It has been shown in dogs that the gastric secretions excited by insulin hypoglycemia can be completely stopped by full doses of atropine (Babkin,<sup>4</sup>

LaBarre and de Cespedes<sup>15</sup>). Peterson and Peterson<sup>16</sup> employed dibutoline, a derivative of carbaminoylcholine possessing atropine-like qualities, and completely abolished the gastric hyperacidity secondary to insulin hypoglycemia in human subjects. In conditions associated with hyperglycemia it might be expected, then, that the gastric juices are of low acidity and peptic power. That this is so is suggested by the low incidence of peptic ulcer among patients with diabetes mellitus as reported by Jankelson and Rudy,<sup>17</sup> Bowen and Aaron,<sup>8</sup> and Rothenberg and Teicher.<sup>11</sup>

The parasympathetic and sympathetic nervous systems of the body are reciprocal in function. When one of these nervous systems is blocked or overly stimulated the normal balance is upset. Illustrative of this is a patient reported by Blegen and Kintner.<sup>7</sup> Following a dorsolumbar sympathectomy for hypertension, his pre-existing gastric ulcer became active. The release of the sympathetic control allowed the parasympathetic (vagus) to stimulate the gastric glands unchecked. Interruption of both these nervous pathways in the same individual will have a neutralizing effect in those organs supplied by them. Weeks, Ryan and Van Hoy<sup>20</sup> reported a case of hypertension and peptic ulcer in which a combined dorsolumbar sympathectomy and vagotomy was performed. The benefits to be expected by release of vagus control of the stomach were nullified by the removal of the sympathetic influence, as the patient finally had a perforation of the ulcer.

**Method of Study.** For the purpose of this study 5 patients with schizophrenia, to whom insulin shock therapy was being given, were selected. A fasting blood sugar and gastric analysis was done on each and was repeated at  $\frac{1}{2}$  hour intervals until the conclusion of the shock period. There were 4 females and 1 male, ranging in age from 20 to 37 years. Unfortunately, a fractional gastric study had been made on only 1 patient prior to treatment. Three of the patients had had glucose tolerance tests before treatment, and

1 had had no pertinent laboratory studies. In obtaining the gastric samples a Levine tube was passed by the nasal route and was allowed to remain in place during the test. Blood sugar estimations were done using the micro-sugar technique of Folin-Wu, modified by Fiorentino and Giannettasio,<sup>9</sup> and were read in a photoelectric colorimeter.

Sweating and irritability of varying degrees were taken as evidence of insulin shock and were noted in all the patients. However, true coma with loss of contact to such stimuli as calling the patient by name and shaking his shoulders was not always achieved. This was particularly so when the smaller insulin dosages were used. Regular insulin was used in all the cases.

**Report of Cases.** CASE 1 (Fig. 1). A. M., a white female, age 36, with hebephrenic schizophrenia. At the time of beginning treatment she weighed 190 pounds and had a fasting blood sugar of 125 mg. %. Insulin therapy had been begun 3½ months before this study was made, so that at the time of observation the daily dose of insulin was 450 units. The results of the tests are shown graphically in Figure 1. It will be noted that the gastric acidity exceeded the normal values on only 2 occasions. However, in each case as the blood sugar values decreased, the gastric acidity increased. With the blood sugar blood was noted grossly or chemically in all the gastric samples except those collected during the last day of observation. On this day the insulin dosage had been reduced and the patient was suffering from a mild upper respiratory infection. Nausea and vomiting after termination of shock was a daily feature in this patient. With this history and the finding of blood in the gastric contents a fluoroscopic examination of the upper gastro-intestinal tract was done but no evidence of ulcer could be determined. It was believed that she had a hemorrhagic gastritis due to the increased gastric acidity.

CASE 2 (Fig. 2). N. J., a 23 year old white female with simple schizophrenia. At the time of institution of treatment she weighed 110 pounds, and had a fasting blood sugar of 74 mg. % and a slightly increased glucose tolerance. In each instance as the blood sugars fell the gastric acidity increased.

There were no complaints referable to the gastro-intestinal system.

CASE 3 (Fig. 3). J. M., a 20 year old white male with catatonic schizophrenia weighed 145 pounds. Insulin therapy had been started 4 days prior to the first test. He had had a fasting blood sugar of 100 mg. % before treatment and a gastric analysis which showed 18 degrees free and 16 degrees combined acid in the fasting state, increasing to 40 degrees free and 8 degrees combined 3 hours after the alcohol test meal.

Despite the fact that the blood sugar values never reached extremely low levels and coma was not attained, the gastric acidity increased sharply as the blood sugar levels fell. As suggested by Kepler and Moersch,<sup>12</sup> it would seem that the vagal stimulation resulted more from a rapid decline in blood sugar than from its actual value at any one time. The gastric samples in the last 2 tests contained blood in all but the fasting specimens. There were no symptoms of nausea or vomiting at any

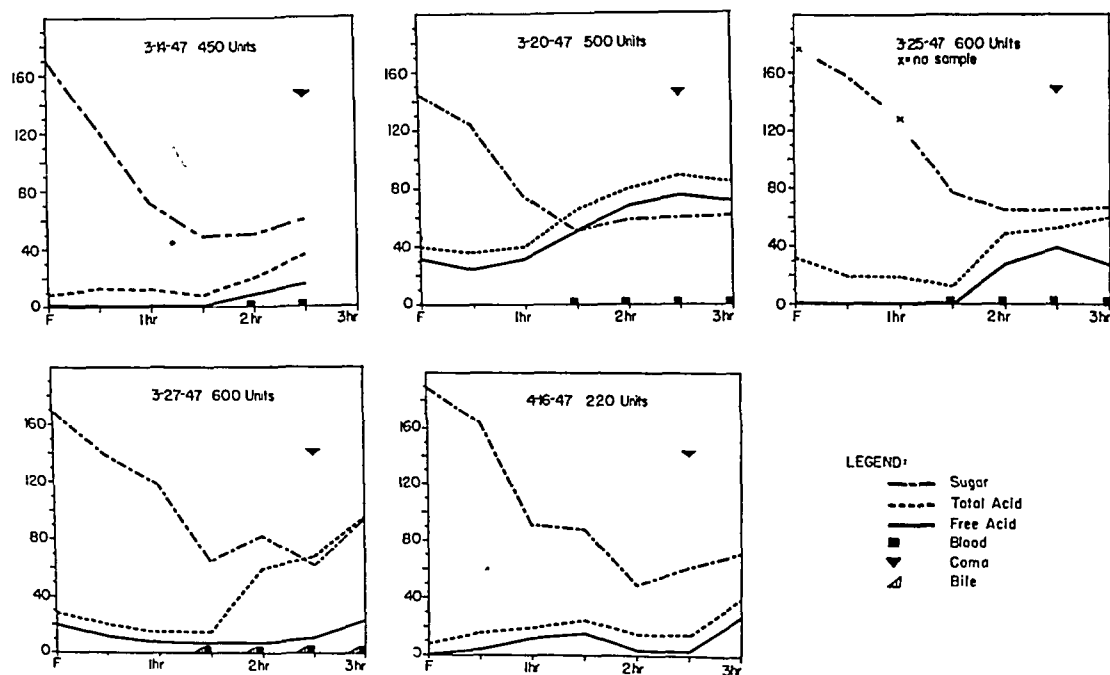


FIG. 1.—Case 1, A. M.

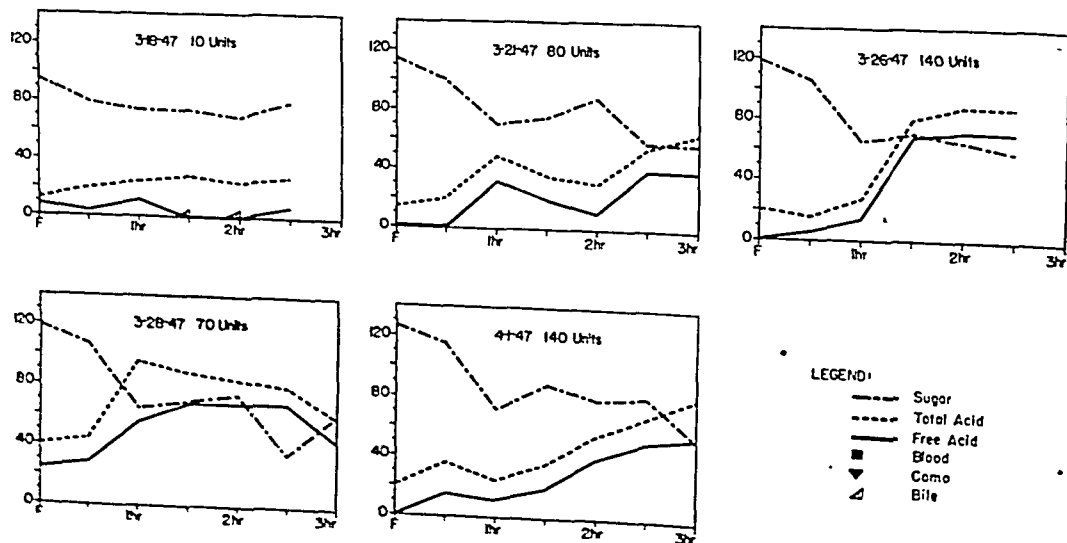


FIG. 2.—Case 2, N. J.

time. No gastro-intestinal Roentgen rays were made.

CASE 4 (Fig. 4). B. L., a 21 year old white female with catatonic schizophrenia weighed 138 pounds. Glucose tolerance tests prior to insulin therapy showed fasting levels from 103 to 119 mg. % with return to fasting levels in 3 hours. The stage of coma was reached in each test in from 2 to 2½ hours. A constant and pronounced gastric response followed the drop in blood sugar values. The free HCl rose to the neighborhood of 100 de-

grees in practically every trial. No symptoms of gastric irritation were noted.

CASE 5 (Fig. 5). G. M., a 37 year old white female with paranoid schizophrenia had had 2 previous courses of insulin therapy. Decided improvement in her condition was noted following each, but she would relapse after several months. At the time of beginning the last course on insulin she weighed 136 pounds. Insulin had been started approximately 2 months before this study was made. Although the actual degree of eleva-

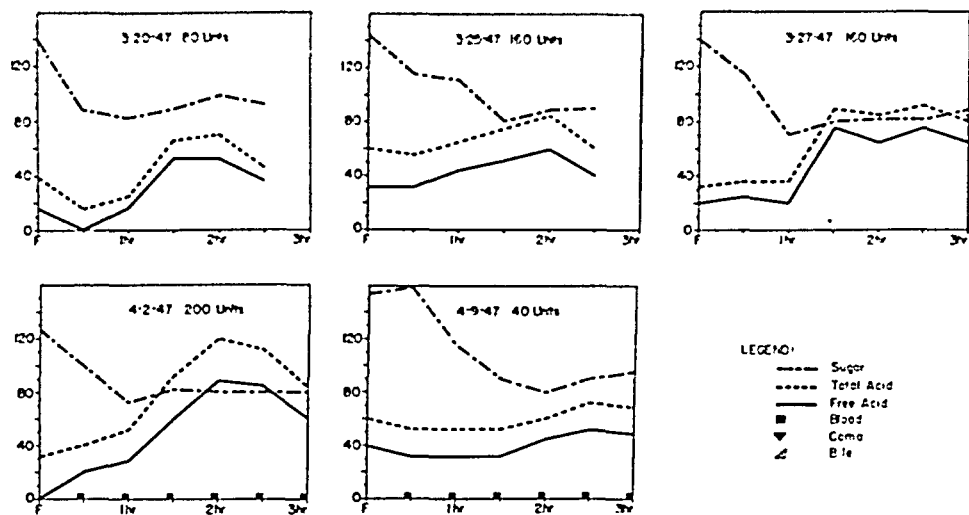


FIG. 3.—Case 3, J. M.

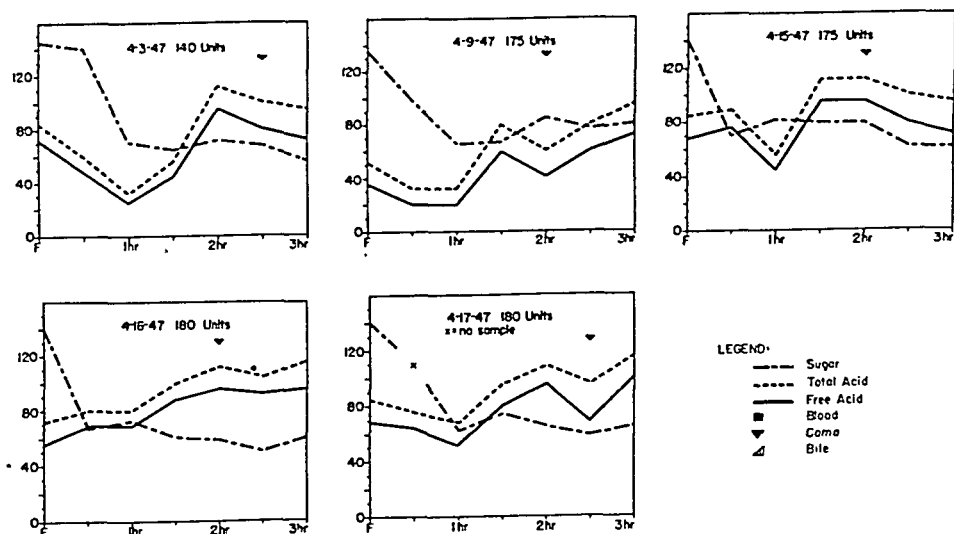


FIG. 4.—Case 4, B. L.

tion of gastric acidity was not constant in each test, a definite trend of increase in both free and combined acid was seen as the blood sugars declined. The unstable emotional status of the patient is reflected in the fluctuating values recorded on 2 occasions.

effort to avoid such a complication it is suggested that thorough gastro-intestinal studies be made on each patient before beginning insulin therapy. Those patients in whom the suspicion or diagnosis of ulcer

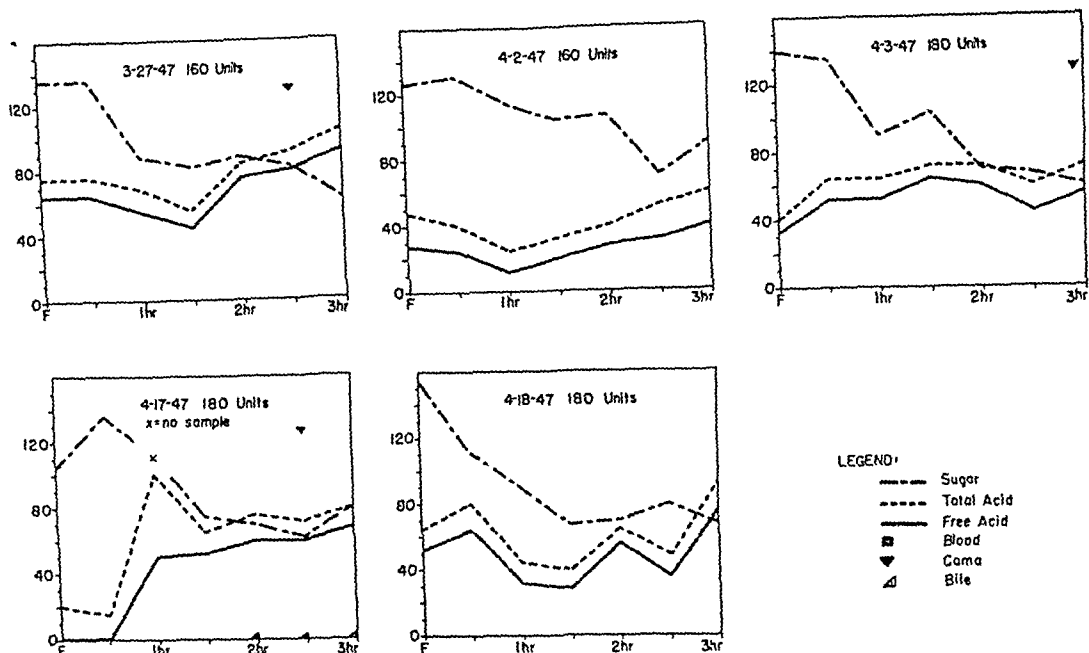


FIG. 5.—Case 5, G.M.

A possible explanation of the high values for fasting blood sugars noted in each of the cases may lie in the fact that 3 patients were given insulin shock daily, except Sunday; and were fed very high carbohydrate beverages each day to terminate the shock.

**Comment.** The cases illustrate the effect of hypoglycemia upon gastric secretion. It was shown that when the blood sugar values were decreased the acid content of the gastric juice increased. The vagus nerves have been shown to be concerned in the mediation of such stimuli.

Gastric hyperacidity is believed to be one of the contributory factors in the production of peptic ulcer. Mental patients given insulin shock treatments over long periods of time have at the same time a high degree of gastric acidity and are, therefore, made more liable to the development of gastric or duodenal ulcer. In an

exists should be protected against the ensuing alteration of the gastric contents. This should include measures to reduce vagal action in the stomach, such as full atropinization, or even vagotomy in proven ulcer cases. Measures to combat the gastric acidity by neutralization and buffering of the gastric contents with antacid preparations during the periods of hypoglycemia should be employed also.

**Summary.** 1. In 5 cases of schizophrenia given insulin shock treatment a definite increase in the acid content of the stomach occurred during the periods of hypoglycemia.

2. Thorough gastro-intestinal studies should be completed in such patients before giving insulin, and measures to counteract or nullify the gastric secretory response to hypoglycemia should be instituted.

This work was carried out while serving as Teaching Fellow in Medicine, The Elizabeth Steel Magee Hospital, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

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## MULTIPLE ATTACKS OF MENINGITIS

## REPORT OF A CASE WITH AUTOPSY

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BEFORE the advent of serum therapy it was extremely unusual for anyone with pneumococcic meningitis to survive. But now specific antisera are seldom required and may be difficult to obtain. However, with the widespread use of chemotherapy and antibiotics the fatality rate for this severe infection has greatly decreased. Nevertheless, it is rare for persons to have more than 1 attack of meningitis, although with intrathecal treatment, relapses or recurrences due to the same infecting organism may occur.

Bronstein<sup>1</sup> reported the case of a man who had 4 attacks of meningitis in a period of 8 years, but 2 of these episodes could well have been relapses rather than reinfections. On 2 occasions the illness was attributed to the meningococcus but no organisms were found the other times. This patient died; there was no autopsy. Craddock and Bower<sup>2</sup> also reported a case in which a woman had 4 attacks of meningitis in 1 year and recovered. On the first occasion, pneumococci Type XVII were identified, but in the second attack culture of the spinal fluid was reported sterile. The third time a pneumococcus, Type XXVIII was disclosed but in the fourth instance the spinal fluid was sterile, as in the second attack. Thus it would appear that this patient had two distinct infections, each with a recurrence. During the past year we had a patient with pneumococcic meningitis on our service who had one relapse while convalescing in the hospital from his original attack. Later he returned home apparently well but after 1 week was readmitted with a second relapse which resulted in his death.

On many occasions when establishing a diagnosis of pneumococcic meningitis we have been impressed with the patient's history of a skull fracture or head injury at some remote time. One<sup>4</sup> of us reported 3 patients with second attacks of pneumococcic meningitis occurring at intervals of about 6 months to 1 year. Two of these patients had histories of skull fractures which antedated the meningitis by 1 year or more. In each case the infecting organism was of a different type in the 2 attacks. All 3 patients recovered; none had any intrathecal treatment. Traut<sup>5</sup> had a patient who had meningitis 5 times with recovery and in this case there was a history of skull fracture 2 years previously. On the first 3 occasions the organism was pneumococcus Type XXI, which suggests that 2 of these attacks were recurrences rather than new infections. With the fourth illness no organisms were found but when the fifth attack took place, pneumococci Type XV were responsible. The patient recovered. Fox<sup>3</sup> reported 1 patient with relapsing meningitis due to pneumococci Type XXIX and another with recurrent meningitis caused by meningococci. Nearly all of the patients reported with multiple attacks of meningitis have been adults. However, 2 of the 3 cases with second attacks of pneumococcic meningitis which were observed by one<sup>4</sup> of us involved children.

We wish to report an instance in which the patient had meningitis 5 times within a period of 5 years. On each occasion a different organism was found in the spinal fluid. When the patient expired following his fifth infection, the autopsy finding



clearly afforded an explanation for the vulnerability of the meninges.

**Case Report.** L. S., a 30 year old structural iron worker, was first seen at Cook County Contagious Disease Hospital on Oct. 10, 1912. The history was that of an upper respiratory infection for about 3 weeks. He had gone to work as usual on the day of admission. At 5 p.m. of that day his wife found him at home in a stupor and had him removed to a private hospital where a diagnosis of meningitis was made and he was transferred then to Cook County Contagious Disease Hospital. The only significant event in his past history was a fall from a scaffold, in 1931, for which he was hospitalized. Roentgen ray films of the skull at that time did not disclose any fracture.

*Physical examination* revealed a well-nourished, white male who was stuporous, but thrashed wildly about. Temperature was 103.6° F. rectally; pulse, 120; respirations, 28; blood pressure, 130/80. There was marked nuchal rigidity and the Kernig and Brudzinski signs were positive. Tendon reflexes were absent but the remainder of the physical examination was essentially negative. Because the patient was unmanageable, it was necessary to administer 250 mg. of sodium pentothal in order to sedate him and then a lumbar puncture was made, with the following results: spinal fluid, cloudy; pressure, 440 mm., water manometer; cell count, 4000, polymorphonuclears predominating. Culture of spinal fluid showed pneumococci Type XXV. Spinal fluid glucose was 68 mg.; protein, 375 mg.; chlorides, 68 mg. Kahn test was negative. Urine was negative, and the white blood count was 10,300.

The patient was given immediately 5 gm. of sodium sulfathiazole intravenously plus parenteral fluids and at the end of 24 hours this treatment was repeated, the 5 gm. of sodium sulfathiazole again being given intravenously. Heavy sedation was required to keep the patient from tossing about. He was put on a 4 hour schedule of 2 gm. sodium sulfadiazine in 100 cc. of distilled water intravenously and was given 100,000 units of Type XXV antipneumococcus serum intravenously. The temperature rose to 106° F., respirations became labored and oxygen was required. The following day another 100,000 units of specific serum was

given intravenously and a third injection of 100,000 units was made 8 hours later. He remained stuporous all day and his temperature fluctuated from 102° to 103.6° F. rectally. The next day, his 5th in the hospital, he received 300,000 units more of serum intravenously and that night he became rational and was able to answer questions. Sulfonamide medication was then administered orally and the remainder of his hospital stay was uneventful. The meningeal signs gradually subsided and he went home asymptomatic on the 25th day after he entered the hospital.

*Second Admission* (Mar. 30, 1943). This time the patient entered the hospital in a comatose condition. He had complained of headache for about 6 hours and had vomited 6 or 8 times. Physical examination showed a restless comatose male with a temperature of 105° F. rectally; pulse, 140; respirations, 40; again the only positive physical findings were nuchal rigidity and positive Kernig and Brudzinski signs. Lumbar puncture revealed a cloudy fluid with increased pressure, cell count of 24,000, predominantly polymorphonuclears; spinal fluid culture was reported positive for pneumococci Type X; spinal fluid protein was 300 mg.; chloride, 680 mg., and glucose, too low to obtain reading. He was started on intravenous sodium sulfapyridine, 5 gm., and 30 minutes later 4 gm. more of the same drug intravenously. Intravenous fluids, and paraldehyde for sedation, were also given. In addition, 150,000 units of Type X antipneumococcus serum was injected intravenously. His maintenance dose of sulfonamide consisted of sulfadiazine, 2 gm., at 4 hour intervals intravenously until the 4th hospital day when he was rational enough to be put on oral medication. He was discharged asymptomatic on the 14th hospital day.

*Third Admission* (Oct. 20, 1943). On this occasion the patient was irritable when he entered the hospital but was able to give a history of headache and pain in the back of his neck for about 20 hours and vomiting 5 or 6 times within the past 4 hours. Physical examination was essentially negative except for a rigid neck; temperature, 103° F.; pulse, 120; respirations, 40. Lumbar puncture showed purulent fluid with a cell count of 2400, predominantly polymorphonuclears; protein of 225 mg.; glucose, again too low to read; chlorides of 710 mg.

Culture of both the blood and spinal fluid revealed *H. influenzae*. He was treated with intravenous sulfathiazole, 5% glucose intravenously, and repeated blood transfusions, getting 500 cc. whole blood daily for 3 days. At times he would become maniacal and had to be heavily sedated. On the 4th day he was able to take oral medication and was put on sulfapyridine, 2 gm. every 4 hours. By the 10th day he was alert, asymptomatic and against all medical advice signed his release and left the hospital.

*Fourth Admission* (Feb. 21, 1944). Again the patient was brought into the hospital in a semicomatose condition with a history of "running nose" and a cough the night before. He went to work complaining of a headache but returned home 2 hours later and became "wild" and soon lapsed into semicoma. Physical examination was essentially the same as on previous admissions. Temperature, 104° F. rectally; pulse, 128; respirations, 32. Lumbar puncture showed opalescent fluid under increased pressure. Spinal fluid glucose was 30 mg.; protein, 375 mg.; chlorides of 660 mg. Both blood culture and spinal fluid culture were positive for pneumococci Type XI. The patient was given sodium sulfamerazine, 9 gm., intravenously, continuous 5% glucose by vein and sedation as on previous admissions. Two gm. of sodium sulfamerazine were given intravenously every 8 hours until the 4th hospital day when the drug was administered orally. On the 2nd hospital day he received 400,000 units of Type XI antipneumococcic serum intravenously. He became progressively better and went home at the end of 12 days. Just before he left the hospital Roentgen rays of the paranasal sinuses were taken and they showed clouding of the ethmoid and sphenoid sinuses. No specific therapy was instituted for this latter condition.

*Fifth Admission* (April 16, 1947). Once more the patient came to the hospital irrational. History was that of headaches for 8 hours and extreme restlessness for the past 4 hours. He had made the comment to his wife the night before, "I guess I'm coming down with meningitis again because spinal fluid has been dripping from my nose." One other fact which may be of some significance is that he was struck on the face with a rivet while at work about 1 week prior to entrance. Physical findings were of

the same nature as upon previous admissions; temperature, 104° F. rectally; pulse, 140; respirations, 30. Lumbar puncture showed a pressure of 440 mm. water manometer; the fluid was cloudy with a positive Pandy and cell count of 5310 polymorphonuclears. Smear disclosed many gram positive extracellular diplococci. Culture of spinal fluid revealed pneumococci Type XX; spinal fluid glucose of 8 mg.; protein of 450 mg. Urine showed 4+ albumin with many red blood cells and white blood cells per high power field; white blood cell count, 17,500; red blood cells, 4.4 million with 80% hemoglobin.

Ten thousand units of penicillin in 10 cc. of saline were instilled intrathecally and this was repeated daily for 4 days. In addition the patient was given 40,000 units of penicillin intramuscularly every 3 hours and an initial dose of sodium sulfadiazine, 6 gm. intravenously; 1½ gm. of the same drug were injected every 4 hours intravenously. Continuous intravenous fluids were given and sedation as before. Patient remained in coma for 4 days, temperature rose to 106° F. and he expired on the 4th hospital day. Total medication over a 4 day period was 40,000 units of penicillin intrathecally, 520,000 units of penicillin intramuscularly, and 41 gm. of sodium sulfadiazine.

*Summary of Autopsy Findings.* The body was that of a well-developed and well-nourished white male who weighed 63 kg. and 173 cm. long. The pupils were round and equal, not dilated or constricted. The peritoneal cavity was free of fluid; the serosal surfaces smooth and glistening. The lower pole of spleen was at the ninth rib in the midaxillary line. The liver was 3 cm. below the costal margin and 8 cm. below the xiphoid. Both halves of the diaphragm were at the level of the fourth rib.

The pleural cavities were free of adhesions; the pleura smooth and shiny. The pericardial sac contained 15 cc. of straw colored fluid. The lungs were both crepitant, their cut surface dark purple and red and wet. On pressure a large amount of frothy fluid escaped. The trachea and bronchi were lined by a congested and edematous mucosa.

The heart weighed 300 gm. The valves were normal, the muscle good; the coronary arteries showed a few fatty plaques.

The liver weighed 1400 gm.; the capsule

was smooth and shiny, the consistency firm; on section lobular markings were distinct.

The gall-bladder and ducts were normal.

The spleen, pancreas, adrenals were not remarkable.

The kidneys weighed 350 gm. total. The capsule stripped with ease, leaving a smooth surface. On section, the markings between the cortex and medulla were distinct. Sulf crystals were present in the renal pelvis. Bladder and prostate were normal.

The brain weighed 1250 gm. Over its convexity, near the pons, and around the vermis of the cerebellum, there was yellowish pus along the course of the blood-vessels. Over the left parietal and occipital lobes was an extensive subarachnoid hemorrhage, 10 by 8 cm. There was moderate atrophy of the gyri of the frontal lobes, the remainder of the gyri were markedly flattened and the sulci shallow.

The skull showed 2 small perforations behind the Crista Galli which led to the ethmoid air cells and into the nasopharynx.

**Summary and Comment.** 1. Five attacks of meningitis are a great rarity.

2. On 4 occasions the infecting organism was a pneumococcus, each of a different type. In 1 instance *H. influenza* was responsible for the meningitis, a form of meningitis that seldom occurs in adults.

3. On 4 occasions, including the attack of influenzal meningitis, the patient recovered without intrathecal treatment or frequent taps for drainage of cerebral spinal fluid. In the first attack there was 1 lumbar puncture before admission and 1 after; only 1 puncture was made during each of the next 3 infections. In the fifth and fatal attack there was a daily puncture<sup>4</sup> with intrathecal penicillin until death.

4. During the fatal illness, therapy included the administration of penicillin intrathecally. At autopsy there was an extensive subarachnoid hemorrhage over the left parietal and occipital lobes. It seems possible that intrathecal penicillin may have contributed to this complication.

5. The autopsy disclosed a ready pathway for intracranial infection: 2 small perforations behind the Crista Galli leading into the ethmoid air cells and so to the nasopharynx.

6. In every case of pneumococcic meningitis it is advisable to have roentgenograms of the skull with special reference to the sinuses.

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# PROGRESS OF MEDICAL SCIENCE PEDIATRICS

UNDER THE CHARGE OF  
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## CLINICAL APPLICATIONS OF BONE MARROW EXAMINATION IN CHILDHOOD

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THE number of reports on what can be learned by bone marrow examination has grown impressively since Arinken's<sup>1</sup> first description of sternal aspiration in 1929, less than 20 years ago. This Review outlines briefly those features of marrow examination which are of practical importance in clinical pediatrics. Emphasis is given to the more recent contributions—the contained bibliographies refer back to earlier papers. For more detailed surveys of the marrow in infancy and childhood the reader is referred to the primary articles by Vogel and Bassen<sup>45</sup> ("Sternal Marrow of Children in Normal and in Pathologic States"), Diwany<sup>10</sup> ("Sternal Marrow Puncture in Children"), Shapiro and Bassen<sup>40</sup> ("Sternal Marrow Changes During the First Week of Life"), Kato<sup>20</sup> ("Sternal Marrow Puncture in Infants and in Children"), Smith<sup>41b</sup> ("Blood Disorders in Infancy and Childhood"), and others. An excellent critical survey of techniques, normal values and sources of error is that of Osgood and Seaman<sup>33</sup> ("The Cellular Composition of Normal Bone Marrow as Obtained by Sternal Puncture"). This deals with children as

well as with adults. An abundance of data can also be found in every good textbook of hematology, such as the recent ones of Whitby and Britten,<sup>46</sup> Wintrobe<sup>47</sup> and Kracke.<sup>21</sup>

To evaluate and interpret the findings in an aspirated specimen of marrow one must be aware of the limitations of the approach as well as its positive worth as a source of information. The procedure is done so differently in different clinics and the range of normal variation is so great, that it is not wise to draw precise comparisons between one report and another or between normal and questionably borderline states. Many of the principles and standards employed are of a statistical rather than of an absolute nature. The pathologist and clinician when examining a specimen should know: (a) The bone from which the specimen comes; (b) The manner of collecting and preparing the specimen; (c) The limitations of the method; (d) The age of the child and normal conditions at that age; (e) The disease the patient is suspected of having; (f) The patient's peripheral blood picture; and (g) The significance of any changes

which may be encountered, such as (1) hyperplasia or (2) hypoplasia of any or all of the normal cellular elements, (3) infiltration or proliferation of abnormal cells, (4) presence of protozoan parasites.

**Preliminary Considerations.** **BONE FROM WHICH THE SPECIMEN COMES.** It has long been known that during the first few years of life the marrow of practically all bones is red and cellular. Fat cells begin to appear between the ages of 5 and 7 years. With progressing age the active marrow recedes gradually from the distal portion of the skeleton toward the trunk until, at about age 18, active hemopoiesis takes place normally only in the vertebrae, ribs, sternum, skull, innominate bones, and proximal epiphyses of femur and humerus.

In the premature and newborn the sternum, the tibia or the femur may be used as the source of marrow. After early infancy the sternum has proved almost universally the site of choice. It is easy of access, and its marrow remains free from the normal fatty changes which affect the long bones as the child grows. Diwany<sup>10</sup> and Kato<sup>20</sup> have devoted much attention to the pattern of growth in the sternal centers ("sternebrae") from the standpoint of facilitating marrow punctures. The ossification centers of the sternum appear at the sixth month of intrauterine life, first in the manubrium then in the other sternebrae. The centers appear in pairs, one on each side of the midline; in each segment the pair of centers later fuse into a larger one. At birth the manubrium already displays one large fused mass, whereas the next three segments contain small paired centers separate from each other. Fusion of the centers is not always regular and uniform; pairing may persist in the lower segment of the sternum as late as the twelfth year. Puncture in children should always be done opposite an interspace, in order to avoid the cartilaginous partitions which separate the sternebrae.

**MANNER OF COLLECTING AND PREPARING THE SPECIMEN.** "The ideal method of obtaining marrow specimens would permit

removal of a large representative, measured specimen in such form that accurate cell identification and counts of each type of cell may be obtained and all structural relationships could be observed" (Osgood and Seaman<sup>23</sup>). Unfortunately, no such ideal method is feasible. The available techniques for collection of marrow fall into two classes: (a) procurement of a button of marrow by trephine; (b) aspiration through a needle.

The button of marrow secured by biopsy permits the ready preparation of both imprint and microscopic sections. Microscopic sections preserve cell relationships and include all type of cells. Disadvantages<sup>3</sup> are the necessity for using the operating room, the longer time in arriving at a full report, the residual scar, and the possibility of missing patchy lesions. Differential counts may be grossly in error; in a transverse section only unidentifiable segments of some cells will appear, and small cells can be obscured by other overlying cells. Needle aspiration is simpler to perform and is widely employed in pediatrics. Cell morphology is excellent. Unfortunately the anatomic positions of the various cells in relation to each other are not reconstructable and all cells are not always equally aspirated. Aspirated peripheral blood may confuse the picture. Suspensions can be made to obtain quantitative total nucleated cell counts which give a rough idea of the cellularity of the marrow, and the smears enable one to make accurate cell identification and differential cell counts.

**LIMITATIONS OF THE METHODS.** Differences in technique of dealing with aspirated marrow lead to wide variations in the final counts. This makes comparisons of the findings of different authors confusing. As Osgood and Seaman<sup>23</sup> comment: "Any article purporting to give the data on marrow of normal individuals should state the number, age, sex, race, criteria of health, geographic locality where the study was made, the altitude, and the general nutritional status of the subjects examined, as well as indicate

whether the women studied were pregnant or non-pregnant and, in the case of the latter, the relationship of the time of obtaining the marrow to the menstrual cycle."

Doan and Zerfas<sup>11</sup> summarize the difficulties encountered in the study of the bone marrow: "Any attempt at a quantitative estimation of the various cellular elements making up the bone marrow must, in the very nature of the survey, always be open to many questionings: the limitation inherent in any technique used, the fallacies inescapable in trying to draw any general deductions from even 1000 or 2000 cells counted out of the multiple millions present in any functioning bone marrow, the much debated questions of identification and classification of immature forms, the many factors known and unknown affecting hemopoiesis in any particular individual; all of these and more make it necessary to be conservative in the drawing of deductions from any one limited series of observations or in trying to compare the figures obtained from different investigators."

AGE OF THE CHILD AND RANGE OF NORMAL VALUES FOR THE AGE. A number of authors have attempted to determine the marrow picture of normal children at various ages. Such surveys have been reported by Tecilazic,<sup>42</sup> Kato,<sup>20</sup> Vogel and Bassen,<sup>45</sup> Veneklaas,<sup>44a,b</sup> Shapiro and Bassen,<sup>40</sup> Diwany,<sup>10</sup> and others. Osgood and Seaman<sup>23</sup> have recently compiled the findings in children in terms of a uniform nomenclature. Interested readers are referred to the original authors and the paper by Osgood and Seaman for exact data.

The general distribution of marrow cells in the normal child may be summarized as follows: Nucleated red cells will range from 12 to 25% of all nucleated cells; eosinophils, 2 to 6%; lymphocytes, 5 to 35%; granuloblasts (myeloblasts), 1 to 4%; other myeloid cells of the granulocyte series, 40 to 60%; miscellaneous (megakaryocytes, reticulum cells, plasma cells, monocytes, basophils, etc.), 0 to 6%.

These ranges are valid for children of all ages, from the premature and newborn up through puberty. They represent the usual findings, not the extremes of normal variation. Osgood and Seaman comment that the differences in differential cell counts in children and adults are relatively slight compared to the variations in the figures of different investigators for the same age group. If there is any significant difference between children and adults it is a slightly higher percentage of granuloblasts (myeloblasts) and progranulocytes (promyelocytes) and a slightly lower percentage of neutrophil lobocytes (polymorphonuclear neutrophil leukocytes) in children.

It must be borne in mind, too, that considerable variations, especially quantitative, may occur in a given case in different stages of the disease, where repeated examinations are being made.

Certain generalizations have been made by several workers, which seem indicative of positive trends. On the day of birth, the percentage of erythroid elements is high, 30 to 65%, and falls steadily during the first week so that by the seventh day it may be only 12 to 40%.<sup>40,42</sup> This reflects the curtailed production of new red cells. The percentage of myeloid cells goes up in reciprocal relationship.

In Kato's<sup>20</sup> series, the small lymphocytes predominated over the myeloid elements in the first 2 months. The majority of these lymphocytes were small, with heavily condensed nuclear chromatin and scanty basophilic cytoplasm. Typical blood lymphocytes of the medium and large varieties were rarely found in the marrow of young infants. In the erythro-genic series the majority of cells were fairly mature normoblasts. Karyorrhexis, Howell-Jolly bodies and Cabot rings were not found in normal infants and children. Megaloblasts were also consistently absent. The myeloid-erythroid ratio was lower for infants and children up to 4 years than for older children and adults.

The total number of cells per unit volume of aspirated marrow appears to

be higher in infants and young children than in the older age groups.<sup>10,31</sup> The values for total nucleated cell counts per cubic millimeter of sternal marrow average about 150,000 to 300,000, with normal variation as low as 50,000 and as high as 1,000,000 (Vogel and Bassen).<sup>45</sup>

Children have a slightly higher percentage of myeloblasts and promyelocytes and a slightly lower percentage of neutrophils than do adults.<sup>30,46</sup> In prematures this tendency is more marked; the marrow is usually more hyperplastic and immature in prematures than in full term infants.

**THE SUSPECTED DISEASE AND THE PERIPHERAL BLOOD PICTURE.** The blood picture is not always an accurate reflection of the histologic status of the marrow.<sup>6</sup> The peripheral blood may show all the features suggestive of a hypoplastic marrow such as anemia, leukopenia or thrombocytopenia, individually or in combination, and yet the marrow on examination may prove to be crowded with the respective families of cells, or exhibit aplastic or hypoplastic changes, aleukemic leukosis, invading lymphosarcoma or other neoplasm, or Gaucher's disease. Thus, the physician must have both types of information available, in order best to appraise the positive findings.

The limitations of marrow examination might make it seem as if the procedure had but little clinical value. This is not the case; with increasing experience it is becoming more and more valuable. These limitations do emphasize, however, the importance of observing all the recognized precautions, if the results obtained are to be relied upon.

**Significance of Changes. HYPERPLASIA OF THE WHITE CELL COMPONENTS.** The cells of the myeloid series tend to proliferate during most *acute pyogenic infections*, usually with an increase of more immature cells.<sup>39</sup> The degree of immaturity seems usually to parallel the stage and severity of the infection. In *infections associated with peripheral neutropenia*, the leukocytic elements of the marrow may be either increased or decreased.

In *infectious mononucleosis* Freeman<sup>15</sup> reported infiltration of the marrow with abnormal cells similar to those in the blood stream. Vogel and Bassen<sup>45</sup> and others,<sup>31</sup> however, failed to corroborate this. Limarzi, Paul and Poncher<sup>25</sup> have recently described sternal aspiration in 25 cases of infectious mononucleosis. Their patients ranged in age from 13 months to 35 years. The marrow was nearly always hyperplastic with an increase in immature granulocytes but without proliferation of atypical lymphocytes. Toxic granulations were seen in many of the neutrophilic myelocytes but not in the metamyelocytes. The blood neutrophils showed toxic granulation and a moderate shift to the left. The authors suggest that in this disease a noxious factor affects many of the myelocytes and prevents their differentiation to neutrophils, leading instead to the development of toxic band forms. This behavior of the marrow contrasts with that in lymphatic leukemia, in which characteristic replacement with leukemic cells takes place regardless of the blood findings. Sternal puncture thus becomes an important aid for differentiating benign from malignant types of lymphocytosis.

In *acute infectious lymphocytosis* the outstanding feature in the marrow is the increased number of normal small lymphocytes.<sup>41a</sup> Myeloid elements and nucleated red cells are normal in quantity. The values in 2 patients, aged 5 and 9 years, were 43 and 42% lymphocytes, respectively, as compared with the more usual lymphocytic range of 15 to 25%.

In *smallpox* Schretzmayer and Lancaster<sup>37</sup> found in the marrow both a rise in immature myelocytes and a "characteristic" increase in cells of the reticulo-endothelial system, plasma cells and reticulum cells. At times there was also an increase of the lymphocytes, corresponding to the lymphocytosis generally present in the blood.

In *Banti's syndrome (chronic congestive splenomegaly)* myeloid hyperplasia has been described in the earliest stages when the peripheral blood shows a moderate

anemia and leukopenia.<sup>41b,42</sup> Later the marrow findings consist of a "maturation arrest" of the myeloid and megakaryocyte tissues. In the final stage normoblastic hyperplasia also appears.

In *pertussis* Landolt<sup>22a</sup> found, in a study of 12 children, that the marrow tends to be hyperplastic, with numerous eosinophils and immature myelocytes. There was no increase in the lymphocyte content of the marrow: the proportion of lymphocytes ranged from 9 to 22% (average 15.5%) though samples of peripheral blood at the time of marrow examination had absolute lymphocyte counts up to 43,000.

**HYPERPLASIA OF THE RED CELL COMPONENTS.** Hyperplasia of the red cell elements is a regular feature of *hemolytic anemias*. Wintrobe<sup>47</sup> states that in these disturbances as many as 60% or more of the nucleated cells in smears of sternal marrow as obtained by puncture or biopsy may belong in the erythrocytic series. Smith<sup>41b</sup> thinks that nucleated red cells in excess of 50% of all the nucleated cells of the marrow constitutes an important diagnostic feature in hemolytic anemia. Smith finds the marrow hyperplastic in the hemolytic anemias with an increased proliferation of normoblasts and to a lesser extent of erythroblasts. Granulopoiesis may also be active. In iron deficiency anemia and in chronic hemorrhagic anemia granulopoiesis is normal.

Most authorities<sup>17,23,39,47</sup> agree that in *iron deficiency anemia* the bone marrow contains an excess of nucleated red cells. These are largely normoblasts; few if any megaloblasts are found. Scott,<sup>39</sup> for example, describes the erythroblasts as increased to a degree roughly proportional to the anemia. The predominant and characteristic cell is a small mature polychromatic normoblast having an irregular and jagged cell outline with a small rim of slate-grey cytoplasm around the pyknotic nucleus. According to Scott, when this cell dominates in erythropoiesis; an iron deficiency may be inferred. With onset of treatment the erythroblasts increase steadily until a peak is reached

parallel with the maximal reticulocytosis in the peripheral blood.

In *congenital hemolytic jaundice (spherocytic anemia)* Limarzi<sup>23</sup> noted the bone marrow to be hyperplastic at the normoblastic stage. Leukopoiesis is also increased. Following splenectomy the number of normoblasts decreases. Scott<sup>39</sup> found in this condition a great increase in erythroblasts, which form 50 to 75% of the cells in the puncture films. There appears to be little correlation between the erythroblast percentage, the degree of anemia, and the peripheral reticulocytosis. There is no change in the erythroblasts to foreshadow the abnormal shape of the mature red cell.

In *Mediterranean (Cooley's) anemia* the bone marrow is hyperplastic with many parent stem cells, nucleated red cells, myelocytes and megakaryocytes.<sup>47</sup> Some phagocytes contain small amounts of hemosiderin. Foam cells present in small islands may give an appearance resembling Gaucher's disease.

As for *erythroblastosis fetalis* due to Rh incompatibility, Potter<sup>34</sup> comments that the bone marrow in most infants studied at the Chicago Lying-in Hospital series has been hyperplastic (as described also by other observers), but in a few infants the marrow could not be distinguished from that of an unaffected newborn. Occasional irregular areas are found in which blood cells are completely absent and the spaces between the trabeculae filled with mucoid connective tissue. Potter suggests that the progressive anemia in erythroblastosis fetalis may be due in part to the bone marrow remaining hypoplastic when blood formation stops in the liver after birth.

In *sickle cell anemia* authorities are agreed that the marrow shows pronounced augmentation of normoblastic activity.<sup>23,45,47</sup> Limarzi<sup>23</sup> states that the marrow shows similar findings whether the spleen has been removed or not. Wintrobe<sup>9</sup> describes the marrow as consisting largely of nucleated red cells, chiefly normoblasts. Some polychromatophilic normoblasts and



more immature forms may occur. There may be a moderate "shift to the left" in the myeloid leukocytes, and eosinophils may be relatively numerous. Megakaryocytes may be present in increased number, monocytes may contain ingested red corpuscles, and nuclear fragments as well as pigment granules may be scattered about. In several specimens Wintrobe has observed long, filamentous bands of what appears to be erythrocytic cytoplasm which may extend across the whole oil-immersion microscopic field.

In *ankylostomiasis with anemia* Diwany<sup>10</sup> found marked changes in 9 of 10 children studied. Erythroblastic and normoblastic hyperplasia was marked. The cytoplasm of the nucleated red cells was commonly basophilic or polychromatic and numerous mitotic figures were seen in almost every case. Eosinophils were invariably present. This picture is described as resembling that in post-hemorrhagic anemia and is compatible with the view that ankylostomic anemia is due to chronic blood loss. In long-standing ankylostomiasis with severe anemia Schretzmayr and Lancaster<sup>37</sup> found the pattern to change to that of an aplastic marrow corresponding to the other signs of aplasia, *e. g.*, general wasting, muscular atrophy, and a dry thin skin.

Zuelzer and Ogden<sup>50</sup> have directed attention to a form of macrocytic anemia, designated *megaloblastic anemia*, seen in 25 infants. A characteristic dysplasia is found in the marrow, with both erythropoiesis and leukopoiesis being affected in a manner similar to pernicious anemia. The precursors of the red cells show "prevalence of 'young' basophilic and polychromatic cells; limitation of mitotic activity, mainly to the earliest stages of maturation; abnormal karyokinesis, with tripolar or multipolar mitoses and atypical chromosomes; an abnormal nuclear structure, which stamped these cells as megaloblasts in the restricted morphologic meaning of the term . . .; lobulation and distortion of the shape of the nuclei; an increased tendency to denucleation by

karyorrhexis and sometimes by karyolysis, and an increase in the size of the cells and in the relative amount of cytoplasm at all levels of maturation." The granulocytes have a similar "shift to the left;" they are usually enlarged and their nuclei often hypersegmented. The characteristics of the circulating blood are a normochromic and usually macrocytic anemia, leukopenia, neutropenia and thrombopenia. The patients exhibit a specific response to a hemopoietic factor contained in liver extract, folic acid concentrates and pure folic acid.

ALTERATIONS IN MEGAKARYOCYTES. Alterations in the megakaryocytes have not been deemed of much pediatric significance except in *hemophilia* and the *purpuras*. Limarzi, Poncher and Birch<sup>26</sup> reported on the marrow findings in 4 patients with hemophilia. During the remission phase there was a normal quantitative and qualitative pattern for the erythroid, myeloid and megakaryocytic elements. During the bleeding phase, in contrast, the marrow was hyperplastic and the mature megakaryocytes were increased.

Nickerson and Sunderland<sup>32</sup> comment that in the marrow from patients with *idiopathic thrombocytopenic purpura hemorrhagica* marked variation is seen, not only between different cases but in repeated specimens from the same case. A distinct increase of young forms is noted, together with a slight increase in adult forms, and a corresponding diminution of degenerating megakaryocytes. Dameshek and Miller<sup>7</sup> described megakaryocytes as being moderately increased in acute purpura hemorrhagica, but with diminished platelet production; following splenectomy, platelet production became more active. Schwartz<sup>38</sup> commented that spontaneous recovery is more likely to take place when the eosinophils in the marrow are plentiful. He studied 30 patients with "primary" thrombocytopenic purpura, and found that they could be grouped into two types: (a) those with increased number of eosinophils in the marrow (above 50

per 1000 granulocytes); (b) those with no increase in marrow eosinophils (below 50 per 1000 granulocytes). Of 14 patients with low counts only one recovered spontaneously, whereas 12 of 16 patients with high marrow eosinophil counts recovered spontaneously. He suggested that the high eosinophilia is a manifestation of an allergic state, and that patients having high eosinophil counts owe their thrombocytopenia to sensitization or "allergic" phenomena.

**HYPOPLASIA AND APLASIA.** Aplasia and hypoplasia of the entire bone marrow system must be rare in childhood, since one finds few references to the condition in this age period. The precipitating causes in adults may be benzol, organic arsenicals, gold compounds, radio-active substances, irradiation with roentgen rays, and other chemical and physical agents.<sup>47</sup> These offenders can doubtless give rise to the same disturbance in exposed children.

Diwany<sup>10</sup> describes a generalized depression of the bone marrow in 2 children with *cretinism*. The main feature was the low total count, indicating marrow hypoplasia. In 1 patient, aged 12 years, the total nucleated cell count which had been 40,000 per c.mm. rose to 190,400 after 1 month's treatment with thyroid preparations. The nucleated red cells showed very slight rise—from 11.2 to 15%; the blood hemoglobin from 30 to 60%. Depression of the bone marrow is viewed as a manifestation of the general slowing down of all metabolic processes which occurs in hypothyroidism.

Diamond and Blackfan<sup>9</sup> describe a form of *congenital chronic anemia* as "hypoplastic." This disturbance is characterized clinically by anemia and production of reticulocytes at an extremely low, almost negligible, rate. Such children require repeated transfusions at regular intervals for maintenance of life. In 4 cases, Blackfan and Diamond described the marrow as being in "moderate hypoplasia."

Fanconi,<sup>14a</sup> Dacie and Gilpin<sup>5</sup> and Win-

trobe<sup>47</sup> have reported instances of a *familial anemia* characterized by pigmentation of the skin, hypoplasia of the gonads, and developmental anomalies. These patients exhibited anemia, leukopenia, thrombocytopenia and underactivity of the bone marrow.

Estren and Dameshek<sup>13</sup> have described a familial "*chronic hypoplastic anemia*." Examinations of the marrow, carried out in 3 of 6 siblings in one family and 5 of 14 siblings in another, revealed marked hypoplasia with a decreased number of megakaryocytes. Granulopoiesis and erythropoiesis were orderly and qualitatively normal but quantitatively markedly diminished. -

Whitby and Britten<sup>46</sup> comment that when the bone marrow is partially replaced by implants of foreign tissues or by an overgrowth of the bony tissue proper, the remaining or adjacent marrow may be stimulated or irritated into excessive myeloid and erythropoietic activity. The changes that may be found in the peripheral blood include an anemia that is sometimes severe and a variable leukocytosis, that is not often great, but composed partially of a number of primitive myeloid cells. The descriptive title of *leuko-erythroblastic anemia* has been suggested by Vaughan.<sup>43</sup> The red cell changes are characterized not so much by anemia as by the appearance in the blood of young red cells and nucleated forms—a "shifting of erythropoiesis to the left."

In "*marble bone disease*" (*Albers-Schönberg disease*) an aplastic or myelophthisic anemia develops in about one-fourth of the cases.<sup>43</sup> Similar marrow changes may occur in *osteogenesis imperfecta* and other congenital bone diseases.<sup>12</sup>

**DEPRESSION OF WHITE CELL COMPONENTS.** The cells of the neutrophilic<sup>8,30a,b</sup> series are the first and most often affected in *sulfonamide reactions*. The value of bone marrow studies in such agranulocytic manifestations has been discussed fully by Smith,<sup>41b</sup> who points out that the bone marrow is the site of origin of the myeloid elements and the place where the full

extent of damage to the mature granulocytes and their precursors may be examined at first hand. The toxic effects of sulfonamides on the bone marrow are represented by varying degrees of suppression of granulocytic elements and at times by a diminished total cellular content. In mild injury both promyelocytes and myelocytes are present, whereas the severe and fatal type presents an arrest in development at the myeloblast stage with a complete absence of more mature granular cells. If marrow examination reveals that myelocytes and more mature polymorphonuclear cells are numerous, the sulfonamide therapy need not be discontinued if the need for it is urgent. Repeated bone marrow studies are required, however, to guard against a sudden shift to an immature level. A marked reduction in the more mature elements and an increase in stem cells and in lymphocytes calls for immediate withdrawal of the drug. With recovery, myelocytes make their appearance in increasing numbers and are followed by more mature neutrophils.

Replacement of the bone marrow by blast cells, as in leukemia, does not occur in *leukemoid reactions*.<sup>47</sup>

Haden,<sup>17</sup> Hynes<sup>18</sup> and Wintrobe<sup>47</sup> point out that a marrow examination aids greatly in the study of a patient with *leukopenia*. If the granulocytes are absent due to some drug, the marrow may contain an abundance of immature myeloid cells, largely late myelocytes and metamyelocytes, owing to interference with maturation. In the early stages of agranulocytosis the cellularity is normal but practically all the myeloid cells are myeloblasts. If death takes place from sepsis with partial remission of the blood picture, the marrow is hyperplastic and crowded with young neutrophils. When the disease has lasted for some days, the myeloblasts may disappear, leaving lymphocytes and plasma cells as the only leukocytes in the marrow.

**CELLULAR INFILTRATIONS.** Any disease characterized by dissemination or pro-

liferation of reactive cells throughout the body can be expected to show involvement of the marrow, particularly since the marrow has an abundance of reticulo-endothelium. The diseases in which aspiration of marrow can accordingly serve as an aid in diagnosis of suspected cases are the leukemias, neoplasms and disturbances of cellular lipid metabolism.

**Leukemia.** Leukemic cells predominate in the bone marrow in leukemia.<sup>17,18,39,41b,45</sup> Involvement is usually diffuse but may be nodular or patchy. Vogel and Bassen,<sup>45</sup> for example, have described the marrow in 12 children with acute leukemia. Acute lymphatic leukemia was characterized by practically entire replacement of the normal cells with lymphoblasts and lymphocytes (over 95%). Acute myeloid leukemia was characterized by replacement with myelocytes and myeloblasts (over 95%). There was an associated diminution of the red cell and megakaryocytic elements.

Sternal puncture is of especial value in the recognition of "aleukemic" leukemia. The marrow may be highly cellular, filled with leukemic cells. In some cases the cellularity has been found reduced without any change in the differential count.<sup>39</sup>

When the peripheral blood count is high in the thousands, it may be impossible to be certain that the puncture films represent marrow rather than blood, since the marrow composition may not be significantly different from peripheral blood.<sup>39</sup> One expects to find more blast forms in leukemia than in the hyperplasia of simple leukocytosis. Hynes<sup>18</sup> states that in leukemia the production of red cells is depressed with the percentage of erythroblasts being almost equal to that of normoblasts. This "maturation defect" is probably associated with the macrocytic anemia which often accompanies leukemia.

In acute cases it may be difficult to distinguish between lymphoblasts, myeloblasts and monoblasts. Cells of intermediate maturity and mature cells help in the identification. Scott<sup>39</sup> comments that the finding of over 40% of lymphocytes in the marrow suffices for a positive

diagnosis of lymphatic leukemia, whereas a normal count does not exclude the condition.

*Neoplasms.* Infiltrations of the marrow by metastatic tumors are thoroughly familiar to the roentgenologists, who do not hesitate to make the diagnosis from the roentgen shadows of affected bones. Landolt's<sup>22b</sup> recent report describes marrow aspirations in 47 children with cancer (mostly sarcoma and neuroblastoma). In neuroblastoma the characteristic tumor cells were recovered from the bone marrow in 11 of 16 cases examined, thereby establishing the diagnosis. In these patients many macrophages were present in the marrow, and macrophage mitosis was observed. With reticulum cell sarcoma the sarcoma cells were identified. Even when no tumor cells were recognized in the smear, an increase in reticulum cells and immature myeloid cells usually suggested the diagnosis. Smith<sup>41b</sup> states that with neuroblastoma, clusters of primitive cells can be observed in the counting chamber which appear in the films as large immature cells forming syncytial masses simulating a mosaic pattern.

In *Hodgkin's disease*<sup>9,31</sup> the bone marrow findings have been variable and non-specific. Lesions are focal rather than diffuse. There may be a shift to the left in the myeloid series, a slight monocytosis or moderate eosinophilia, and a relative reduction in nucleated red cells.

In 6 cases of *lymphosarcoma* in Hynes'<sup>18</sup> series the marrow was normal. In 1 other case, associated with a chronic macrocytic anemia, sternal puncture produced marrow containing 51% small lymphocytes, 10% lymphoblasts, and only 14% mature neutrophils. At autopsy the bone-marrow and other organs were extensively infiltrated with lymphosarcomatous nodules.

Rubinstein<sup>35</sup> has described a 15 year old boy with a pathologic fracture of the femur, in whom sternal marrow aspiration gave the first clue to the correct diagnosis of *multiple myeloma*. Repeated sternal aspirations yielded a marrow of low cell count (18,000 to 41,000 in 1 cm.), with 8

to 25% plasma cells in the differential count. Otherwise there was normal cell distribution. The plasma cells displayed mitotic figures with double nuclei, multiple nucleoli, uneven staining, and vacuolization of the cytoplasm.

*Disturbances in Cellular Lipid Metabolism.* In *Niemann-Pick's disease*<sup>46</sup> typical large lipid-filled cells are seen which are round, oval, or polyhedral and filled with a web of hyalin droplets. *Gaucher's disease* exhibits nests of characteristic large foam cells, 20 to 80 micra in diameter;<sup>41b</sup> the cells are round, oval or spindle-shaped and usually possess one or many small eccentrically placed nuclei. The cytoplasm stains faintly or not at all with fat stains. Examination of the sternal marrow of a 10 year old boy with Gaucher's disease by Chalmers<sup>2</sup> revealed a hyperactive cellular marrow with an increase of erythroblasts and normoblasts and numerous Gaucher cells. Leukopoietic elements were reduced. In essential xanthomatosis of the normo-cholesteremic type—Hand-Schüller-Christian disease—aspirated marrow will be free from xanthomatous cells unless a lesion is aspirated directly. Young and Osgood<sup>48</sup> report a negative finding in a sternal puncture done shortly after death in a boy of 5 years with xanthomatosis of the Hand-Schüller-Christian type. The sternal marrow had escaped the infiltration present in the marrow of other bones and in many other tissues as demonstrated at necropsy.

**Bacteriologic Examinations.** In this country, sternal puncture has not been utilized to any extent as a device to recover organisms in obscure bacterial infections. In other countries the method has long been employed for finding the etiologic agents in typhoid fever, brucellosis, streptococcal septicemia, subacute bacterial endocarditis, lobar pneumonia, tuberculosis and other infections. A few representative reports are here cited.

In a patient with staphylococcus septicemia, Ling, Hsueh *et al.*<sup>27</sup> found that sternal marrow cultures yielded a positive growth in 24 hours whereas blood cultures

done at the same time were not positive until 48 hours.

Crisculo<sup>4</sup> has reported on culture of the sternal bone marrow in 14 acute cases of brucellosis. The *Brucella* organism was isolated from the blood in 10. In 11 patients cultured during the early stages of the disease, 8 presented positive blood cultures and 7 positive sternal marrow cultures. In an acute case with a gradual onset 3 months prior to hospitalization the sternal culture was positive; a year later, during an afebrile period when the condition had become chronic, the culture was negative.

Ling *et al.*<sup>28</sup> performed 110 sternal marrow and cultures simultaneously with 38 patients diagnosed as having typhoid or paratyphoid fever. Both marrow and blood cultures showed positive growth in 31 instances, and both were negative in 33. Marrow cultures yielded a positive growth in 44 instances in which the blood cultures were negative, whereas in only 2 instances did marrow culture fail to demonstrate the organism when the blood culture was positive. Success in this approach was attributed to the fact that in typhoid fever the reticulo-endothelial cells phagocytize the organisms. Inasmuch as the bulk of the reticulo-endothelial system lies in bone marrow, spleen and liver the invading organism is demonstrable in those organs in large numbers. Marrow puncture is easier and safer than splenic or hepatic puncture.

**Protozoa.** Protozoan parasites may be demonstrable in aspirated marrow when the peripheral blood seems free of their presence. The usefulness of this approach has been especially evident with kala-azar, malaria, and trypanosomiasis. Histoplasmosis, toxoplasmosis<sup>16</sup> and torula infections should be recognizable also by marrow aspiration. Success is largely due to the large amount of reticulo-endothelium in bone marrow.

Chung<sup>3</sup> has reported on 171 cases of kala-azar diagnosed by sternal puncture. The majority of the patients were in the first two decades of life; many were infants

under 1 year. As many as 40 Leishman-Donovan bodies could be seen in each oil immersion field. Many of the patients were also subjected to splenic and hepatic puncture. Sternal puncture gave the highest percentage of positive results.

Schretzmayer and Lancaster<sup>37</sup> have described both a myelocytic and an erythroblastic increase in chronic malaria—the latter change in response to the anemia. Proliferation of proerythroblasts and megakaryoblasts are similar to the findings in pernicious anemia. Gigantic band-forms and hypersegmented leukocytes may appear. Examination of the marrow for parasites reveals many more sexual forms than in the blood. In subtertian malaria gametocytes may be numerous in the marrow though absent from the peripheral blood. Active mitosis may be observed there, as well—a process practically never observed in the blood. Rumball and Parsons-Smith,<sup>36</sup> and Yu and Ying<sup>49</sup> corroborate the higher percentage of success in demonstrating parasites in marrow.

The marrow of 5 children with urinary bilharziasis was examined by Diwany.<sup>10</sup> Four showed a moderate eosinophilic reaction ranging between 10 and 15. The fifth revealed a high eosinophilia in the peripheral blood (70%) and in the marrow (60%).

Linhard<sup>29</sup> repeatedly studied 40 patients with trypanosomiasis and uncovered the parasites more frequently in the marrow than in the peripheral blood, the ratio being 211:129.

*Histoplasmosis* may be demonstrable by marrow examination, as in the infant reported by Iams and Keith.<sup>19</sup> The fungus parasites were seen free in the tissue fluid as well as inside monocytes, immature neutrophils, megakaryocytes, eosinophils and large phagocytic reticulo-endothelial cells.

**Cystine Disease.** The presence of free cystine crystals in aspirated marrow of affected children has been demonstrated by Fanconi.<sup>14b</sup> In fact, this approach is recommended as the method of choice for rapid diagnosis in suspected cases.

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## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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## CURRENT TRENDS IN OBSTETRIC ANALGESIA

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THE purpose of this paper is to present the current trends in obstetric analgesia and anesthesia. Continuous caudal analgesia, introduced in 1942 by Hingson and Edwards,<sup>16</sup> has received more attention than any method of analgesia since the Twilight Sleep of Kroenig and Gauss. Demerol, a recently synthesized analgesic drug, has been tested in obstetric patients. The use of spinal anesthesia for the late stage of labor and delivery has been revived. Psychic control of the pain of childbirth has been reported. Further observation of the older methods of pain relief has more clearly defined their usefulness.

This discussion will be limited to the methods of analgesia and anesthesia currently in use in obstetrics. Special attention will be paid to their basic advantages and disadvantages without regard for the merits of the many technical variations. Safety for mother and infant will be the principal criterion of evaluation. The effectiveness of pain relief, and the practical requirements of administration will be considered.

**Analgesia Prior to Delivery.** *Narcotics.* Morphine and related compounds have been used extensively because of the analgesic effect, the absence of serious maternal reactions, and the ease of administration. The respiratory depressant effect on the newborn has been

demonstrated to be a serious disadvantage. Mengert<sup>28</sup> noted immediate post natal distress in 25% of mature infants, and a higher rate of distress in premature infants subsequent to the administration of moderate doses of morphine to women in labor. The maximum respiratory depressant effect on the infant was observed when delivery took place in the third hour after the use of morphine.

Irving<sup>19</sup> observed a high incidence of fetal respiratory depression following the administration of pantopon to parturient women. He expressed the opinion that the use of narcotic drugs for the purpose of obstetric analgesia was not in the best interest of the infant. Prematurity was considered to be a definite contra-indication to their use. A less important disadvantage was noted to be the failure of effective pain relief in about 30% of patients.<sup>19</sup>

*Demerol.* The investigation of Demerol for the relief of the pain of childbirth was suggested by its analgesic effect,<sup>4</sup> and by the reported absence of significant respiratory depressant action.<sup>35</sup> Clinical experience with the drug in obstetrical patients has been sufficient to warrant an estimate of its value and limitations.

No serious maternal reactions have been noted subsequent to the administration of Demerol,<sup>8,10,33,43</sup> but about 25% of patients have exhibited minor unpleasant reactions *i. e.*, nausea, vomiting, dizziness, dryness

of the mouth, or sweating. No fetal mortalities were ascribed to its use,<sup>8,10,38,43</sup> but some degree of depression of respiration of the newborn was observed. Fetal resuscitation was necessary in from 9%<sup>8</sup> to 16%<sup>38</sup> of newborns whose mothers received demerol. The incidence of fetal respiratory depression was no higher in premature than mature infants.<sup>38</sup> Gottschalk<sup>11</sup> noted no evidence of respiratory depression in newborn infants observed from seven to sixty minutes after delivery.

Demerol effected satisfactory analgesia in only 70% of patients;<sup>10</sup> it did not produce amnesia. When the drug was combined with scopolamine, satisfactory analgesia was obtained in 90% of patients,<sup>38</sup> but the incidence of fetal respiratory depression was higher than when demerol was given alone.<sup>8,38</sup> Maternal excitement occurred in only 3% of patients,<sup>38</sup> and was never extreme. The combined use of demerol and scopolamine was found to be the most satisfactory routine analgesic method by the Boston Lying-In Group.<sup>38</sup>

*Barbituric Acid Derivatives.* The barbituric acid derivatives have been administered frequently for obstetric analgesia<sup>37</sup> because of the ease of administration and the excellent amnesic effect. They were usually given orally, but have been administered per rectum,<sup>3</sup> and intravenously.<sup>1</sup>

Serious maternal reactions have resulted from the use of large doses of these drugs. Galloway and Smith<sup>9</sup> observed a shock-like reaction in 0.2% of normal mothers. Respiratory crises were noted in 0.36% of patients by the Boston Lying-In Group.<sup>24</sup> The administration of barbiturates to mothers with active respiratory disease has resulted in death.<sup>45</sup> A less serious but important limitation has been the high incidence of maternal excitement (16.2%).<sup>19</sup> The occurrence of excitement made special nursing care mandatory, and led to the contra-indication of the use of barbiturates in patients with heart disease, or with other medical complications of pregnancy which reduced

physical reserve. The depressant effect on fetal respiration was minimal. Irving<sup>19</sup> reported that 3% of newborns required resuscitation when the mothers were given sodium pentobarbital.

The major advantage has been the effectiveness of amnesia; 86% of patients experienced complete amnesia, and 14% had partial amnesia with the use of sodium pentobarbital combined with small doses of scopolamine.<sup>19</sup>

*Other Commonly Used Drugs.* It is probable that scopolamine has been given to a greater number of obstetric patients than any other one analgesic, or amnesia inducing drug. Usually, the administration has been in combination with other drugs to which it was considered an adjunct. Kirschbaum<sup>22</sup> has made observations upon parturient patients given scopolamine alone. Two maternal deaths occurred in his series of 1,481 patients, but he expressed doubt that the fatalities had resulted from the effect of the drug. No fetal deaths were ascribed to its use; 5.87% of the infants required resuscitation. Extreme excitement was noted in 1% of mothers. The amnesic effect was graded as excellent. Recently Steinberg<sup>41</sup> reported the histories of 4 patients who exhibited edema of the glottis and uvula with serious respiratory embarrassment after the administration of demerol and scopolamine (3 patients) and seconal and scopolamine (1 patient).

The administration of ether rectally has proved valuable as a part of the Gwathmey technique,<sup>14</sup> or as a means to control the excitement of patients given barbiturates. Gwathmey<sup>14</sup> was able to report 20,000 hospital and home deliveries without a resulting maternal mortality. No infant mortalities were ascribed by him to the use of rectal ether, but resuscitation was required in 15% of newborns. He reported satisfactory analgesia in 85% of patients, but others have noted the analgesic effect to be inferior to that observed from the use of barbiturates or demerol. Technical difficulties of rectal



administrations have limited their usefulness.

Paraldehyde, introduced to obstetrics in 1932 by Rosenfield and Davidoff,<sup>32</sup> has a high maternal margin of safety. Depression of respiration and continued sleepiness of the newborn were observed, but no fetal mortalities were ascribed to the drug. The permeation of the surrounding atmosphere with the unpleasant odor of the drug and the difficulties in administration have limited the use of paraldehyde.

*Regional Analgesia.* Cleland<sup>6</sup> demonstrated that sensory pathways from the body of the uterus run through the sympathetic chain and enter the spinal cord at the eleventh and twelfth dorsal segments. Paravertebral sympathetic block,<sup>20,40</sup> has effectively relieved the pain of labor up to the stage where stress is exerted on the vagina and perineum. Direct infiltration in the para-cervical area has been reported<sup>33</sup> to control the pain of the first stage of labor. These methods have not been tried on a large enough series of patients to warrant conclusions about their safety and usefulness.

The continuous epidural administration of an anesthetic agent by the caudal route has been tested. The need for special attendants, skill, and apparatus has limited the method to approximately 30% of all obstetric patients in America.<sup>24</sup> In well equipped institutions, the administration of caudal analgesia was not applicable to approximately 40-50% of patients for one of the following reasons: (a) local contra-indication, *i. e.*, sacral deformity, obesity, skin infection and pilonidal sinus—10%; (b) constitutional contra-indications *i. e.*, central nervous system disease, severe anemia, drug sensitivity, severe hypertension, unsuitable emotional make-up—10-15%; and (c) obstetrical contra-indications *i. e.*, bleeding complications, disproportion, uterine inertia, malpositions including certain breeches and twins, and fast labors—20-25%.

The maternal death rate in patients given caudal analgesia has been reported

to range from 12 in 30,000 to 10 in 15,950 patients.<sup>24,26</sup> No accurate estimate has been made of the incidence of severe non-fatal fall in maternal blood pressure, but a drop in excess of 20 mm. of mercury has been observed in 8% to 30% of patients.<sup>12,18,26</sup> Fetal deaths have been reported secondary to maternal death, or to severe anoxemia associated with a fall in maternal blood pressure.<sup>17,26</sup> The affect of anoxemia on surviving infants has not been evaluated, but the possibility of damage has been amply demonstrated elsewhere.<sup>47</sup> Less serious but major disadvantages were: the failure of pain relief in 10% of patients,<sup>17</sup> the risk of meningeal, or peridural infections,<sup>17</sup> the risk of breaking of a needle in the caudal canal,<sup>26</sup> and the higher incidence of operative manipulation because of the absence of the secondary powers of labor.<sup>24</sup>

The principal advantage of caudal analgesia was the absence of respiratory depression in the newborn. This method has proved of special value to the premature infant. Other important advantages were the dramatic relief of pain, the applicability to patients with respiratory infections, the elimination of need for supplementary anesthesia, and the reduction in maternal blood loss.

*Psychic Control of Pain.* The effective control of pain in childbirth by hypnosis has been reported.<sup>23</sup> Recently Read<sup>30</sup> offered evidence to support the thesis that the pain of labor is conditioned by tension resulting from fear. He has shown that a patient will willingly go through labor without the aid of drugs if her fears have been allayed by a complete understanding of the mechanism of labor. Sawyer,<sup>36</sup> in this country, reported favorably on this means of pain control in the first stage of labor. The safety of the psychic control of pain cannot be denied, but the practical requirements for the successful execution of the method have limited its use.

*Anesthesia for Delivery. Inhalation Anesthetics.* The major maternal hazard from inhalation anesthesia has been the

aspiration of regurgitated liquid or food. In obstetric patients, there is often no control over the time of anesthesia in relation to the time of eating. Mendelson<sup>27</sup> reviewed the records of 44,016 obstetric patients given inhalation anesthetics and noted an incidence of aspiration in 0.15%. Five patients aspirated solid food and two of them died. In patients who aspirated liquid matter, a post anesthetic broncho-pneumonia was observed though no fatalities ensued.

The principal disadvantage of inhalation anesthetics has been the respiratory depressant effect on the newborn due to narcosis, anoxemia, or both. Irving<sup>19</sup> made observations on patients who were not given drugs during labor, but who were anesthetized for delivery with ether and nitrous oxide gas; he noted that 20% of the newborn required resuscitation. The hazard of anoxemia from improperly administered nitrous oxide gas was pointed out by Eastman.<sup>7</sup> Karp and Richardson<sup>21</sup> reported that 4% of infants required resuscitation when cyclopropane was given for delivery. This gas offered less risk to the infant than any other inhalation anesthetic. The disadvantages of cyclopropane were the need for a skilled anesthetist, special equipment, and the more narrow margin of maternal safety as compared with ether, or nitrous oxide.

*Intravenous Anesthesia.* The intravenous administration of sodium pentothal for operative deliveries and cesarean sections has been reported.<sup>15,25,34</sup> No maternal deaths were ascribed to the agent, but the potential hazard of maternal respiratory arrest was recognized. Gross fetal mortality was not increased with its use.<sup>15,34</sup> Hellman<sup>15</sup> noted that the concentration of the drug in the blood of the newborn began to rise about 5 minutes after administration to the mother, and reached equal concentration in 10 to 12 minutes. He recommended that the drug should be given only when delivery can be assured within 5 to 8 minutes after the time of administration. In skilled hands, the advantages were believed to be the

ease of administration and the excellence of anesthesia for obstetric work.

Recently, Allen<sup>2</sup> has reported the intravenous use of a 1% solution of procaine in 5% glucose in water for the relief of pain in the second stage of labor. The method has not been studied enough to warrant evaluation, but it should be pointed out that Allen observed convulsions in a few patients.

*Local Infiltration Anesthesia.* The extensive use of local infiltration anesthesia for vaginal deliveries and cesarean sections has been reported.<sup>5,13,42</sup> Greenhill<sup>13</sup> stated that he could find no report of a maternal death that had resulted from the use of 0.5% procaine hydrochloride for local infiltration anesthesia. Deaths from the use of higher concentrations of procaine, or other drugs used for local anesthesia have been reported.<sup>39</sup> No deleterious effect on the infant has been observed. The safety of this means of anesthesia has excelled that of any other method.

Several disadvantages have limited the more general use of local anesthesia, namely, the practical difficulty in control of a patient in active labor, the failure of satisfactory anesthesia in approximately 15% of patients, and the skill and patience needed to administer the anesthetic agent.

*Spinal Anesthesia.* The most notable recent trend in obstetric anesthesia has been the revival of the use of spinal anesthesia. Prior to 1940, spinal anesthesia had the record of the highest maternal mortality of all anesthetics used.<sup>13</sup> The recognition of the principle that abdominal distention was associated with a high level of spinal anesthesia led to the development of new techniques of administration. The refinements in technique designed to assure a low level of anesthesia were: (a) the use of small doses and more dilute solutions of the anesthetic agent; (b) the use of hyperbaric solutions combined with elevation of the patient to a sitting, or semi-sitting position; and (c) the avoidance of injection of the solution during a uterine contraction.

No maternal deaths from the use of

spinal anesthesia were reported in a recent series of approximately 4,000 patients.<sup>29,31,43,44,46</sup> An extensive study of non-fatal fall in maternal blood pressure has not been reported. Parmley and Adriani<sup>29</sup> reported a mild transient hypotension in 2% of patients given so-called "saddle block." The occurrence of significant hypotension has not been observed in a series of 800 patients given spinal anesthesia for vaginal delivery or cesarean section at this hospital. In the absence of hypotension, no deleterious effect on the newborn has been observed. Other advantages were a wide range of applicability, excellence of anesthesia, minimal number of complications, and reduction in maternal blood loss as compared to the blood loss observed with the use of inhalation anesthesia.

The practical requirements for the safe administration of spinal anesthesia has

limited its use to well equipped institutions. Definite contra-indications were recognized to be: (a) central nervous system disease, old or active, (b) severe anemia, and (c) marked hypertension. The major disadvantage has been the potential hazard of circulatory collapse or respiratory failure in the mother. Other disadvantages noted were: (a) the failure of satisfactory anesthesia in 5% to 10% of patients; (b) the risk of meningeal infection, (c) the risk of post spinal paralysis; and (d) the occurrence of post-spinal headaches in 15% to 20% of patients.<sup>31</sup>

**Summary.** A review of the current trends in obstetric analgesia and anesthesia has been presented. Attention was directed to the principal advantages and disadvantages of agents commonly used for the relief of pain in childbirth.

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## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 21, 1947

**The Measurement of Coronary Blood Flow by the Nitrous Oxide Method.** J. E. ECKENHOFF, M.D., J. H. HAFKENSCHIEL, M.D., M. H. HARMEL, M.D., W. T. GOODALE, CAPT. M.C., M. LUBIN, CAPT. M.C., R. J. BING, M.D., and S. S. KETY, M.D. (The Schools of Medicine, University of Pennsylvania and Johns Hopkins University, and the Medical Division, Army Chemical Center, Maryland.) The nitrous oxide method introduced by Kety and Schmidt for the quantitative measurement of cerebral blood flow in man is applicable to any organ from which truly representative samples of mixed venous blood can be collected. The heart, by reason of

ventricle/min. by the nitrous oxide method. The coefficient of correlation was 0.77. The partition coefficient for nitrous oxide in the dog's heart when calculated from this relationship was 0.97 (s.e. 0.052) whereas it was 1.05 (s.e. 0.013) when determined by *in vitro* experiments. The partition coefficient of 1 was therefore taken for the experiments described below.

Coronary blood flow in the intact anesthetized dog was measured 17 times in 10 experiments by the nitrous oxide method with the coronary venous blood obtained from a catheter inserted into the coronary sinus. The results are sum-

TABLE 1.—COMPARISON OF CONTROL VALUES OBTAINED SEPARATELY BY THE NITROUS OXIDE AND THE BUBBLE METER METHODS

	Nitrous oxide		Bubble meter*	
	Control values	Coeff. var.	Control values	Coeff. var.
No. of expts. . . . .	10	..	10	
No. of observ. . . . .	17	..	19	
Coronary flow cc./100 g./ min. . . . .	71.3	15.7	66.0	13.0
Oxygen consump. cc./100 g./min. . . . .	9.5	19.1	8.8	13.0

\* Am. J. Physiol., 149, 634, 1947.

its homogeneous structure and venous drainage into the coronary sinus, should thus be a suitable organ. The catheterization technic reported by Goodale and Lubin makes coronary sinus blood of the intact dog or of man readily available. The present investigation was made to determine the possibility of adapting the nitrous oxide method to the coronary blood flow of man.

Coronary blood flow was simultaneously measured in the dog directly by a bubble flowmeter<sup>1</sup> and indirectly by the nitrous oxide method. In 15 measurements in 10 experiments, the average bubble meter flow was 63.7 cc./100 g. left ventricle/min. as compared with 67.8 cc./100 g. left

marized in Table 1 and compared with previously reported values obtained by the bubble flowmeter.

The difficulties and limitations of the method as applied to the heart include (1) inability to always get a free flow of blood from the coronary sinus catheter, (2) blockage of venous return into the coronary sinus if the catheter is inserted too far into the sinus, (3) only left ventricular coronary blood flow is measured and (4) untoward pathological changes have been found following catheterization including subendothelial hemorrhages, endothelial ulcerations and cardiac vein thrombosis. The latter defects are felt to be due

in large part to technical mishandling of the catheters.

The method presumably is adaptable to the measurement of coronary blood flow of man but in view of the pathological findings it should be used with great caution until further data on the pathological effects of coronary sinus catheterization are available.

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**A Method of Directly Recording Intra-arterial Pressure During Surgery.\*** L. H. PETERSON, and G. C. RISMAN, Ph.D. (Dept. of Physiol. Med. School, Univ. of Penna.). It has been possible to record and read immediately the effect of each beat of the heart in the brachial artery in over thirty patients to date. This has been done continuously from before anesthesia is given and continued until after the operation has been completed. The method allows mobility and comfort of the patient and does not interfere with any established surgical procedures.

A flexible plastic catheter is injected into the artery through a special twenty-two gauge needle.<sup>1</sup> The needle is then withdrawn. The Lilly capacitance manometer<sup>2</sup> is used as a pick-up and recording is done with an ink writing oscillograph.<sup>1</sup>

The thirty-odd patients mentioned above provided a rather heterogenous group as concerns age, climatic conditions as well as the clinical condition and surgical intervention. There is no typical pre-anesthetic pulse shape; however, certain types are significant, *e. g.*, hypertension or sclerosis without hypertension. The change in blood pressure from spinal anesthesia may be differentiated as to whether the reduction was mainly due to decreased peripheral resistance or cardiac output. The method has been found practical in predicting a tendency for the blood pressure to fall. Visceral reflexes are more easily localized, the mechanical effect of manual respiration is given another guide and the effects of positional changes are easily noted. It has been

practical to immediately alter the surgical or anesthetic course by the effects seen on the pressure pulse curve. A more detailed analysis of the clinical value of this method will be published elsewhere.<sup>3</sup>

#### Catheterization of the Coronary Sinus.

WALTER T. GOODALE, M.D., MARTIN LUBIN, M.D., and WILLIAM G. BANFIELD, JR., M.D., (Medical Division, Army Chemical Center, Md). The following technique was developed in order to make it possible to measure coronary blood flow in the intact dog, and to evaluate the safety and practicality of a similar procedure in man. A standard intravenous catheter, (size 6-10F), inserted through the dog's external jugular vein under light nembutal anesthesia, is directed into the coronary sinus under fluoroscopic control. The coronary sinus ostium of the dog lies just anteromedial to the inferior vena caval opening into the right auricle, postero-inferior to the tricuspid valve, as best seen fluoroscopically in the right anterior oblique view. On entering the sinus around an initial sharp medial turn, the catheter tip passes superiorly and to the left, along the posterior auriculo-ventricular groove, and often beyond a delicate valve into the great cardiac vein. Sometimes the catheter will pass straight into the middle cardiac vein, from a point just inside the coronary sinus ostium, directed along the posteroinferior septal surface toward the apex. The somewhat hazardous injection of diodrast will outline much of the coronary venous system, because of the abundant veno-venous anastomoses. In 50 procedures upon 25 dogs, weighing 28-75 lbs., the mean blood oxygen contents were as follows: Coronary sinus, 3.8 vols. %  $\pm$  1.04 (standard deviation); mixed venous blood, 12.5  $\pm$  3.89; femoral artery, 16.9  $\pm$  1.75. Dogs recovered promptly, unless purposely sacrificed, without any clinical complications attributable to the catheterization. Twenty-four autopsies following coronary

\* Supported by a grant from the Office of Naval Research to Dr. Bazett.

sinus catheterization sometimes showed significant endocardial lesions, including mural thrombi. However, when a small (No. 7) catheter had been gently inserted only 1-3 cm. into the coronary sinus for less than an hour, avoiding forcible reinjection of any fluid through the catheter, no significant lesions were found. These precautions, which appeared to prevent damage from the procedure in dogs, may well be indicated in any similar studies in man.

#### **The International Congress and its Relation to Future International Organization.**

H. C. BAZETT, M.D. (Dept. of Physiol., Univ. of Penna.). International Congresses in physiology started in 1889. They have always been arranged by a self-perpetuating international committee announced but not elected at each Congress. The committee has met only at the Congresses and has functioned only to select the next meeting place. Details are decided solely by the local committee. The spirit of this organization has been soundly international and democratic, and the present committee saw no reason to change the system. However, international organization in the three years between congresses is a complete void based apparently on the assumption that international problems in physiology are non-existent.

There has been informal discussion relative to the addition of an international union of physiology to existing international scientific unions. A whole meeting was scheduled for such discussion at the Oxford congress but unfortunately had to be cancelled. While some of the international committee thought that in addition to itself there should exist an international union, the committee as a whole regarded this question as outside its province.

The formation of an international union is a function of national societies and action should not await the next congress. Many problems require to be settled. UNESCO cannot give financial assistance to a congress in the absence of an international union to administer and control international activities (though some support was provided to the last congress even in the absence of such organization, this was only possible as an interim measure). Thought should be given to the possible subdivision of the subject (biophysics, biochemists, etc.) if congresses are not to become unwieldy. Exchange of equipment, literature and personnel in troubled times could be facilitated as well as the operation and extension of international institutes such as those at Naples and the Jungfrauoch. As individual physiologists we should work for the formation of an international union of physiology.

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# BOOK REVIEWS AND NOTICES

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**SIGNS AND SYMPTOMS: THEIR CLINICAL INTERPRETATION.** Edited by CYRIL M. MACBRYDE, A.B., M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Washington Univ. School of Medicine. Pp. 439; 74 ills.; 6 color plates. Phila.: J. B. Lippincott, 1947. Price, \$12.00.

THIS book approaches diagnosis in the same manner as the physician must approach it when he sees a patient. The first section is devoted to history-taking and the second to a discussion of the production and interpretation of pain. In every following section a symptom or group of related symptoms is presented, the anatomic and physiologic disturbances concerned with the production of those symptoms being scientifically described and the various diseases causing such disturbances being discussed. Each section is written by a specialist in the field presented. Presentations are clear and understandable. Reference to the experimental is frequent.

Not intended as a textbook for physical diagnosis, it does not cover techniques of examination. In general, attention is paid to the patient's complaint and the mode of production of that complaint, not to what the physician might find on examining him. Any student or practitioner will find this book a useful aid in turning his attention and diagnostic tools to the proper spot for locating disease.

The publisher has used a good grade of paper with a glossy finish. The type is clear, and the book as a whole is convenient to read. The illustrations are clear and helpful.

W. S.

**SYMPTOMS AND SIGNS IN CLINICAL MEDICINE.**

By E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Lecturer in Medicine, Univ. of Liverpool. 4th ed. Pp. 463; 346 ills., 69 in color. Baltimore and London: Williams & Wilkins, 1947. Price, \$8.00.

As a manual of physical diagnosis or as a kind of textbook of medicine, this work is equally unsatisfactory. The patient is chopped up into chapters: The Respiratory

System; The Cardiovascular System; The Nervous System, etc. This leads to repetition of certain parts of the examination, and inadequate covering of others. The tongue is discussed in 8 different places; the tonsils are mentioned briefly under Fever; the liver is discussed under the Cardiovascular System, the Digestive System, the Hæmopoietic System, and Radiology.

Every chapter starts with a discussion of symptoms referable to that particular system, then describes and discusses the more common normal and abnormal physical findings, and ends with brief descriptions of a few of the more common diseases involving that system. Little attempt is made to consider the patient as a whole, or to correlate abnormal physical findings with the fundamental pathologic alterations in structure that can produce these signs. Thus the student or clinician is likely to arrive at erroneous conclusions.

This book cannot be recommended as a text for students. It might serve as a handy reference work for physicians whose main interest lies outside the field of Internal Medicine, or as a refresher for those about to take examinations.

H. H.

**NEW FIELDS OF PSYCHIATRY.** By DAVID M. LEVY, M.D., Assistant Professor of Psychiatry, Columbia University. Pp. 171. New York: W. W. Norton, 1947. Price, \$2.75.

THESE Salmon Lectures are in reminiscent vein when they deal with Child Guidance, Delinquency and Social Work. They sketch the early clumsy approaches (1920) of psychologist, social worker, neurologist and psychiatrist to a boy's problem and then point out how all of these specialists have grown in the last quarter century. A few brief points in Educational Psychiatry and in Comparative Psychiatry are well taken. It is when the author comes to Political Psychiatry that he enters a field where there is no experience—certainly psychiatry as an instrument of government in Germany is a new thing on the earth.

E. B.

**A HANDBOOK OF OCULAR THERAPEUTICS.** By the late SANFORD R. GIFFORD, Professor of Ophthalmology, Northwestern Univ. Medical School. Revised by DERRICK VAIL, M.D., D.O. (Oxon.), F.A.C.S. 4th ed. Pp. 336; 66 ills. Phila.: Lea & Febiger, 1947. Price, \$5.00.

It is good news that this very useful handbook of treatment has been revised. While still retaining the advantages of the book's original form, the present author has expanded many of the sections and has brought ophthalmic treatment up to date, particularly by including an excellent section on the antibiotics.

F. A.

**METHODS OF DIAGNOSIS.** By LOGAN CLENDENING, M.D., F.A.C.P., late Professor of Clinical Medicine and History of Medicine, Univ. of Kansas, and EDWARD H. HASHINGER, M.D., F.A.C.P., Professor of Clinical Medicine. Pp. 868; 143 ills. St. Louis: C. V. Mosby, 1947. Price, \$12.50.

THIS treatise combines in one volume a book on physical diagnosis and a text on differential diagnosis. It is divided into 4 parts. In Part 1, the author devotes 50 pages to a discussion of the principles that underlie proper diagnosis: (1) "the judgment of evidence and (2) reasoning according to the laws of logic." Part 2 of the work consists of a discussion of the technique of history-taking and the general procedures used in physical diagnosis. In Part 3, the symptoms and signs of disease processes are discussed according to the organ affected and to the anatomic regions involved. Part 4 is the author's evaluation of the laboratory studies and special procedures that may be used by the practitioner in diagnostic work, including over 100 pages on Roentgen ray diagnosis.

The informal style and the illustrative cases make the book easy reading. The illustrations and drawings are valuable and instructive. A large amount of material is covered, including many references, though many of these references are old. Some of the opinions expressed are controversial and, if critically analyzed, would not be readily accepted by many authorities. For the medical student, the work would serve to supplement but not replace the standard textbooks of medicine or the standard physical diagnosis texts. It is recommended for

practitioners and internists as a handy reference book and as an aid in differential diagnosis.

E. R.

**PROGRESS IN GYNECOLOGY.** Edited by JOE VINCENT MEIGS and SOMERS H. STURGIS. Pp. 552. New York: Grune & Stratton, 1946. Price, \$7.50.

THIS book contains a collection of 70 papers dealing with the progress that has been made during the last decade in all aspects of gynecologic physiology, pathology and treatment. The papers are by 71 different authors, each of whom is an authority on his subject. The reports are succinct and readable statements, averaging less than 8 pages each, and are followed by bibliographies that have been cut "to the bone" but nevertheless remain adequate for reference to source material.

The record thus assembled is a surprising and encouraging documentation of real progress in a field that many have regarded as relatively static in comparison with general medicine and surgery. Not only have many of the new contributions been made during the war years, but there is a surprising width and balance of distribution among all corners of the field. In its conception and execution, the book provides a perspective and an authority that supplement in admirable fashion what the annual year-books have supplied concerning the decade in question.

As the editors hope, it should certainly prove of interest and assistance not only to medical men who have spent the last years in the Armed Forces, but to students and practitioners in general.

C. B.

**PALEONTOLOGY: INVERTEBRATE.** By HENRY WOODS. 8th ed. Pp. 477; 221 figs. Cambridge, at the Univ. Press; New York: The Macmillan Company, 1946. Price, \$3.00.

THIS small manual attempts to give for each of the larger invertebrate groups, of which fossils are known: a short zoölogic sketch, which accentuates the hard parts; an outline of its classification, with some characteristics of a few genera (mainly British); and a survey of its geologic range, with notes on recent distribution. The figures are mainly simple and clear, but without detailed explanations. A remark-



able amount of data is crowded into small compass. But, in attempting to cover so many fields of paleontology<sup>2</sup>, the book gives the impression of a low threshold of satisfaction in each. The technical terms are introduced rather than explained, and the names of the geological formations will be strange to many American readers. The definitions of the groups are so brief as to be of little assistance in identification, and, in fact, many of the statements are so vague, or have so many exceptions, that they confuse rather than instruct. The bibliography is on the whole remarkably well selected, and includes classic studies as well as modern contributions. The manual should be of help to elementary readers, who wish a cursory survey of the subject.

H. B.

**FUNDAMENTALS OF PSYCHIATRY.** By EDWARD A. STRECKER, M.D., Prof. of Psychiatry, Univ. of Penna. 4th ed. Pp. 325; 21 diagrams. Phila.: J. B. Lippincott, 1947. Price, \$4.00.

Over 100 pages and 6 new diagrams have been added in this edition of Dr. Strecker's excellent introductory textbook on psychiatry—a work intended for the general practitioner, the specialist in other fields and the medical student as well as the psychiatrist. There is a new chapter on Further Thoughts about Nomenclature and Classification, in which the author recognizes the limitations of the present system of classification and includes the Army classification in its entirety. He also proposes a tentative classification of psychiatric illness "based on the concept of Reactive Tension. . . The classification is essentially descriptive. It has no etiologic implications." There is another new chapter on Psychosomatic Medicine and Psychiatry, dealing with the subject in broad terms as it relates to all fields of medicine and advocating the teaching of psychiatric principles throughout the four year medical course. Eight pages on treatment in military neuropsychiatry have been omitted, and a short section added on the benefits resulting from war experiences.

The book continues to be one of the best introductions to the field of psychiatry on the market and contains many short illustrative case histories from the author's wide experience. There is less emphasis than previously on metrazol as a therapeutic procedure, which is in line with the current

trend toward the use of electroshock. With the release of restrictions on the use of paper, the present edition is printed with wider margins, larger type, and a better grade of paper, making it more attractive and readable. The book is heartily recommended for all who are interested in obtaining a first glimpse into the field of psychiatry by one of the acknowledged leaders in that field.

E. B.

**PHYSICAL FITNESS, APPRAISAL AND GUIDANCE.** By THOMAS KIRK CURETON, JR., M.A., M.P.E., Ph.D., Prof. of Physical Education, Univ. of Illinois. Assisted by FREDERICK W. KASCH, B.S., M.S., JOHN BROWN, B.S., and W. G. MOSS, Ph.D. Pp. 566; 66 ills. St. Louis, Mo.: C. V. Mosby, 1947. Price, \$6.00.

THIS book represents an earnest attempt to integrate the authors' wide experience with college athletes with current knowledge of physical fitness tests.

The initial chapters deal with definitions of physical fitness and the validity of various fitness tests. Subsequent discussions include bodily configuration in relation to athletic prowess; cardiovascular, respiratory and motor factors, and the conduct of physical training programs.

The point of view of an athletic coach is stressed. Material is arranged as a text, with questions at the end of every chapter concerning the material presented. The authors have not always been well advised from a medical point of view: The name of Draper is not mentioned in the description of constitutional types. Discussion of the ability of patients with organic heart disease to perform athletics would better have been deleted than treated inadequately and sometimes incorrectly.

W. J.

**FATIGUE AND IMPAIRMENT IN MAN.** By S. HOWARD BARTLEY, Ph.D., Prof. of Research in the Visual Sciences, Dartmouth Medical School, and ELOISE CHUTE, M.A., Research Associate. Foreword by A. C. IVY, Ph.D., M.D. Pp. 429. New York: McGraw-Hill, 1947. Price, \$5.50.

THE authors start with several basic concepts.

One is the need for a "personalistic" approach to the study of fatigue. The whole individual must be studied and attention

must be directed toward the "experiencing" of fatigue rather than to reduction of work output as the basic orientation. The authors assume "that human activity is determined and regulated by other than purely energistic considerations."

The second concept is that impairment is a specific tissue condition. "Impairment is seen as referring to the condition of the tissue, which is directly discovered only by physiological and biological analysis. Whereas fatigue is seen as an expression of the organization of the whole organism, which can be described only in personalistic terms."

A third assumption (later supported by some logical analysis and experimental evidence) is that fatigue should be "regarded as an experimental pattern arising in a conflict situation in which the general alignment of the individual may be described as aversion."

After the introduction, the authors present "Various Views on Fatigue." This is done largely through quotations of representative students of the subject. In Chapter 3 there is a discussion of basic concepts which indicate that the authors recognize the need for scientific methodology in devising the experiment. Since they indicate that the subject is basically a psychological one, it might be better to say that there is a need to develop psychometrics as the first approach to the proper study of fatigue. The writers make a bare beginning by attempting to define fatigue by saying what it is and is not.

The next 14 chapters deal with the varied factors, conditions, and techniques of study used by other experimenters. These chapters are developed largely through reference to the work of others. Findings and conclusions are given. Charts and tables are generously employed.

Chapter 17 on "Visual Performance and Fatigue" is a discussion of visual performance apparently based on the authors' knowledge and research although little or no attempt is made to present experimental evidence.

Chapter 18 is on "Conflict and Frustration" and Chapter 19 on "Chronic Fatigue and Related Syndromes", and here again is utilized a summarizing or "high lighting" type of discussion based on the concepts and experimental findings of other students of the subject.

The last chapter (Chapter 20) represents

the authors' "conclusions." The first part of this chapter consists of briefly stated conclusions without attempt at thorough logical argument or the inclusion of supporting experimental evidence. In the second half of the chapter the authors pose a number of questions which need answers if future studies of fatigue are to be really productive.

A list of "Visual Aids," to supplement the material in the book, follows. An author and subject index are properly included.

To summarize, the book can be described as an excellent attempt at drawing together and "high lighting" the findings and conclusions of the major contributions on the subject of fatigue. The authors do not endeavor to evaluate critically the results, techniques, or conclusions described and quoted. Additionally, the authors postulate several basic concepts and show that they appreciate the need for a logical methodology in science, although they only take a partial first step by attempting to define fatigue and impairment. The book should be extremely valuable to future experimenters in the field.

E. W.

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PHARMACOPOEIA OF THE UNITED STATES OF AMERICA. 13th Revision. By Authority of the U. S. Pharmacopoeial Convention meeting at Washington, D. C. Prepared by the Committee of Revision and published by the Board of Trustees. Official from April 1, 1947. Pp. 957. Easton, Pa.: Mack Printing Co., 1947. Price, \$8.00.

THIS country's Pharmacopoeia does not need recommendation or analytical review. It is a standard, and announcement plus the following quotation from its Preface by E. FULLERTON COOK is tribute: "This revision . . . reflects a period of intensive medical development supported by scientific research of a high order and stimulated by the demands of a global war. . . . The scope policy established in 1820 has been meticulously maintained and an effort made to restrict the admissions to the 13th Revision to those therapeutically active agents, germicides, anesthetics, diagnostic agents, and other necessary medical aids, which reflect the best state of medical knowledge of today. . . . For the first time . . . the English titles occupy the leading position. . . . With the basic therapeutic agents now arranged in alphabetical order,

it is possible to follow each drug with its preparations and it is, therefore, unnecessary to list dosage forms in a special paragraph."

E. K.

**A SYNOPSIS OF SURGICAL ANATOMY.** By ALEXANDER LEE MCGREGOR, M.D. Pp. 714; 699 ills. 6th ed. Baltimore: Williams & Wilkins, 1947. Price not given.

By means of thin paper and small print, the author has covered a huge field in a small handy volume. As implied by the title, the book is meant to be an outline of the subject with only brief comment upon each individual topic. Although a book of this type is useful as a method of reviewing for an examination, it is the Reviewer's opinion that it is otherwise of little value. The discussion of each topic is too brief to give satisfactory information to any but the most casual reader. The illustrations are diagrammatic black and white line drawings, and in many cases these are not easily followed owing to their small size. An extensive index to the numerous subjects is provided.

A. R.

**PRACTICAL PHYSIOLOGICAL CHEMISTRY.** By PHILIP B. HAWK, Ph.D., President, Food Research Laboratories, Inc., Long Island City, N. Y., BERNARD L. OSER, Ph.D., Director, Food Research Laboratories, Inc., Long Island City, N. Y., and WILLIAM H. SUMMERSON, Ph.D., Associate Professor of Biochemistry, Cornell Univ. Medical College, New York City. 12th ed. Pp. 1323; 329 ills., 5 color plates. Phila.: Blakiston, 1947. Price, \$10.00.

THE oldest American text in physiologic chemistry celebrates its 40th year with the issue of this new edition. It has been 9 years since the 11th edition was prepared. Because of the rapid advances in certain major fields and in analytical techniques, there has been a complete revision of the subject matter presented.

Many chapters have been entirely rewritten, and all have been reevaluated to conform to current knowledge. The authors have been aided by specialists in the revision of certain sections. Much new material has been added, including many new sections. To list a few: polarographic analysis, electrophoretic analysis of proteins, isotopes, sulfa drugs, metabolic antagonists and anti-

biotics, Warburg tissue-slice procedures, theory and practice of photometric analysis, composition of foods, and vitamins. These new sections are complete in fundamental data and are well documented.

This volume continues to have a most complete selection of selected laboratory methods. New quantitative procedures for blood and urine analysis have been added, including modifications of older methods for photometric determination.

There is no doubt that this edition will continue to merit the popularity of its predecessors.

H. V.

**WHITHER MEDICINE: FROM DOGMA TO SCIENCE.** By ANTONY FIDLER, M.D., Dozent (Associate Professor) of Medicine of the Univ. of Warsaw; Senior Lecturer in Medicine, Polish School of Medicine, Edinburgh. Pp. 115; 7 tables. Edinburgh: Thomas Nelson, 1947. Price, 6/-net.

STATING that this study is largely a philosophic problem, and that "the author has no training in philosophy," the writer proceeds to a critical consideration of the implications and consequences of the materialistic theory of medicine. In his effort to show that present-day medicine is more a set of beliefs than a science, the thesis is discussed in 3 parts: Causal Medicine, The Medicine of Probability, and Conclusions. The conception of health and disease is that it is rooted in the causal theory, and diagnosis is made for the purpose of finding the "cause," *i. e.*, the disease. In The Medicine of Probability, the proposed numerical data system which is employed is more promising for the following reasons: "(1) the range of variation between the samples is smaller than in the classical system, in spite of the handicap of the experimental conditions; (2) it seems that the attainment of probabilities bordering on certainty in respect to individual predictions regarding the duration of life, the duration of disease, and the frequency of their recurrence is more likely to be achieved by means of it." Finally, it is suggested that the biologist's selection of certain data as healthy or diseased be abandoned, and that a new approach based upon the subjective feelings of the individual be made; that the experimental method be adopted and a different classification of clinical

cal material be employed. In an Appendix, as proof of the author's contentions, 7 statistical tables include the analyses of several thousand cases. For an adequate understanding of the thesis, these tables require some detailed consideration. N. Y.

obstetrics concerning which one cannot find some information in this book. It will, therefore, continue to be valuable not only to students and practitioners of obstetrics but, as a ready reference work, for physicians in all fields. C. B.

**THE PRINCIPLES AND PRACTICE OF OBSTETRICS.** By JOSEPH B. DELEE and J. P. GREENHILL. Pp. 1011; 1108 ills., 211 in color. Phila.: W. B. Saunders, 1947. Price, \$10.00.

THE 9th edition of the late Dr. DeLee's well-known "Obstetrics" is the 2nd edition that Dr. Greenhill has prepared. It has been so extensively rewritten and reshaped as to constitute almost a new book. Admirers of the virtues which made DeLee's book traditionally one of the best texts in any language will be gratified to learn that all the old values have been preserved, and new ones added.

One of the most striking new features is a radical change in format. The text has been rearranged in 2 columns per page with the use of clearly readable "London Times" type face. This has apparently permitted the introduction of new textual material and illustrations without adding to the total number of pages. Indeed, the former bulk of the book has been reduced.

The new chapters include an excellent and practical one on erythroblastosis fetalis. Elsewhere, many of the old chapters have been rewritten to bring each subject up to date by incorporating, rather than merely appending the newer knowledge. Brevity and balance in exposition are thus retained.

The emphasis, as formerly, is on the clinical side. But the sections dealing with the anatomic, histologic and embryologic aspects of the field are scholarly in character, and are illustrated with such excellence as to make the work invaluable as a student guide. One could wish the same attention had been given to physiology. This deficiency is, in the Reviewer's opinion, one of the few weak features of the book. It has led, among other things, to the relegation of "Obstetrics and Gynecologic Endocrinology" to a remote chapter, unrelated to and unintegrated with the general subject of obstetric physiology.

There are few matters in or related to

**TECHNIQUES AND PROCEDURES OF ANESTHESIA.** By JOHN ADRIANI, M.D., Director, Dept. of Anesthesia, Charity Hospital of Louisiana; Clinical Assistant Professor of Surgery (Anesthesiology), Louisiana State Univ. Pp. 404; 122 figs. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.00.

THIS book is intended for the beginner in anesthesia, but can also be profitably read by all who are practising anesthesia. The author has outlined not only the technical details of a procedure, but directly opposite the outline he gives in a brief résumé the associated reasons for executing them. He has covered all phases of the subject and includes many helpful suggestions and explanations.

The chapter on Inhalation Anesthesia is very instructive; even the current price of the anesthetic agent is quoted in order to give the student a comparison of the cost of the administration of the various techniques.

The Appendix contains several tables which list choices of anesthesia for various procedures according to complicating clinical conditions. These will be very helpful to the student and beginner. The volume is well indexed and contains adequate references. The drawings and photographs are well done and show definite details. A vast amount of material has been compressed into this book; it can be unreservedly recommended. P. D.

**GYNÆCOLOGICAL ENDOCRINOLOGY FOR THE PRACTITIONER.** By P. M. F. BISHOP, D.M. (OXON.), Lecturer in Applied Physiology, Guy's Hosp. Med. School; Clinical Endocrinologist, Guy's Hosp.; Endocrinologist to Chelsea Hosp. for Women. Pp. 124. Baltimore: Williams & Wilkins, 1946. Price, \$2.00.

THIS short book was written, as the title indicates, not as a textbook of gynecologic endocrinology but as a guide for the general practitioner. It includes brief descriptions of the endocrine control of the menstua.

cycle and the origin and modes of therapeutic administration of the various sex hormones. The etiology of and the therapeutic approach to the usual functional gynecologic disturbances are considered briefly. The author is more optimistic and less fearful concerning the effects of serum gonadotrophin than most American gynecologists. The chapters on pregnancy tests and hormone assays are well written, but perhaps they are granted too much space at the expense of more generous consideration of the various therapeutic indications in the functional disturbances. Of particular value is the appendix dealing with commercial therapeutic agents, their proprietary names, modes of administration, dosage and prices. The book gives one the impression of oversimplification of a very intricate subject, the justification of which is questionable even in the interests of brevity. F. P.

### NEW BOOKS

*Fatigue and Impairment in Man.* By S. HOWARD BARTLEY, PH.D., Professor of Research in the Visual Sciences, Dartmouth Medical School, and ELOISE CHUTE, M.A., Research Associate. Foreword by A. C. Ivy, PH.D., M.D. Pp. 429. New York: McGraw-Hill, 1947. Price, \$5.50.

*Calcific Disease of the Aortic Valve.* By HOWARD T. KARSNER, M.D., and SIMON KOLETSKY, M.D., Pp. 111; 24 ills. Phila.: J. B. Lippincott, 1947. Price, \$5.00.

*Handbook of Psychiatry.* By WINIFRED OVERHOLSER, A.B., M.D., Sc.D., Professor of Psychiatry, George Washington University, and WINIFRED V. RICHMOND, B.S., A.M., PH.D., Late Consultant in Psychology, New Mexico State Department of Welfare. Pp. 252. Phila.: J. B. Lippincott, 1947. Price, \$4.00.

*Sex Power in Marriage.* By EDWIN W. HIRSCH, B.S., M.D. Pp. 218. Chicago: Research Publications, 1947. Price, \$3.00.

*Trichomonas Vaginalis and Trichomoniasis.* By RAY E. TRUSSELL, M.D., Associate in Hygiene and Preventive Medicine, State University of Iowa. Introduction by E. D. PLASS, M.D. Pp. 277; 19 figs. Springfield, Ill.: Charles C Thomas, 1947. Price, \$6.00.

*Electrocardiografia Clínica.* Por el DR. SERGIO ALVAREZ MENA, Instructor de la Facultad de Medicina. Jefe del Servicio de Cardiología de la Catedra de Pathología Médica del Hospital Universitario. Pp. 567; 240 ills. Havana, Cuba: M. V. Fresneda, 1947. Price not given.

*Ocular Therapeutics.* By WILLIAM J. HARRISON, PHAR.D., M.D., F.A.C.S. Associate Professor in Ophthalmology, Jefferson Medical College. Pp. 112. Springfield, Ill.: Charles C Thomas, 1947. Price, \$3.50.

THIS is a compendium of prescriptions commonly used in Ophthalmology. It does not have any advantage over the other books on ocular therapeutics which include not only a resumé of the drugs used but also the standard treatments for various diseases of the eyes. One cannot use this book, for example, to treat a specific ocular condition since disease processes are not listed even in the index. For that reason its usefulness is considerably limited. F. A.

*Morphologic Hematology.* Special Issue No. 1. Edited by WILLIAM DAMESHEK, M.D. Pp. 200. New York: Grune & Stratton, 1947. Price, \$4.75.

*Kompendium der Parasitischen Würmer im Menschen.* VON HANS A. KREIS, Privatdozent der Parasitologie an der Universität Bern. Pp. 136; 70 ills. Basel: Benno Schwabe & Co., 1947. Price, Gebunden Fr. 10.

### NEW EDITIONS

*Bacteriology Laboratory Directions for Pharmacy Students.* Compiled by MILAN NOVAK, PH.D., M.D., Professor Bacteriology and Public Health, University of Illinois. 2nd ed. Pp. 248. St. Louis: C. V. Mosby, 1947. Price, \$2.75.

*Infant Nutrition.* By P. C. JEANS, A.B., M.D., Professor of Pediatrics, State University of Iowa, and WILLIAMS MCKIM MARRIOTT, B.S., M.D., Late Professor of Pediatrics, Washington University. 4th ed. Pp. 495; 36 ills. St. Louis: C. V. Mosby, 1947. Price, \$6.50.

*Rypins' Medical Licensure Examinations.* By WALTER L. BIERRING, M.D., F.A.C.P., M.R.C.P., Edin. (Hon). With the Collaboration of a Review Panel. 6th ed. Pp. 690. Phila.: J. B. Lippincott, 1947. Price, \$6.00.

THIS edition continues to present the subject matter on which there is "a general agreement regarding the material essential for the candidate for licensure." Each chapter ends with a few pages of sample questions. It is presented under 12 headings by 12 collaborators. The treatment is necessarily brief—53 pages for physiology, for example—and sometimes not up to date.

*Recent Advances in Endocrinology.* By A. T. CAMERON, C.M.G., D.Sc.; Professor of Biochemistry, Faculty of Medicine, University of Manitoba. 6th ed. Pp. 443; 71 figs, 3 plates. Phila. and Toronto: Blakiston, 1947. Price, \$6.00.

THIS small but excellent work, like its five predecessors, contains a brief resumé of most of the latest work in the field of endocrinology. Each section is organized about one of the endocrine glands and presents in addition to the new developments made in the study of the physiologic and pathologic processes of each gland the old work which has stood the test of time. Both the classic and the very recent forms of therapy are presented in every instance and every section is followed by a lengthy bibliography, so that one may readily consult the sources of the material used. (J. McC.)

*A Textbook of Clinical Neurology.* By ISRAEL, S. WECHSLER, M.D., Clinical Professor of Neurology, Columbia University. 6th ed. Pp. 829; 162 ills. Phila.: W. B. Saunders, 1947. Price, \$8.50.

THE text is considered in the following parts: Method of Examination, Spinal Cord, Peripheral Nerves, Brain, Neuroses, with almost half the space taken by Brain. The psychoan-

alytic approach is Freudian. Psychosomatic medicine is not discussed. The customary chapters on anatomy and physiology are omitted. All subjects are given concise and practical treatment, with scant reference to the work of others. (N. Y.)

*Synopsis of Allergy.* By HARRY L. ALEXANDER, A.B., M.D., Professor of Clinical Medicine, Washington University. 2nd ed. Pp. 255; 22 ills. St. Louis: C. V. Mosby, 1947. Price, \$3.50.

*Annual Review of Biochemistry.* Edited by J. MURRAY LUCK, HUBERT S. LORING and GORDON MACKINNEY. Vol. XVI. Stanford University P. O., California: Pp. 740. Annual Reviews, Inc., 1947. Price, \$6.00.

THE latest volume in this valuable series continues the excellent tradition and purposes of its forerunners. The end of the war has resulted happily in an increase in the number of contributors from abroad, among them E. G. V. Percival on the Chemistry of Carbohydrates, D. P. Cuthbertson on the Metabolism of Proteins, H. Lundegardh on the Mineral Nutrition of Plants, and D. D. Woods on Bacterial Metabolism.

Besides the usual topics, such as Biological Oxidations and Reductions, this year's review has articles in less customary fields: Carotenoid and Indolic Biochromes by Denis L. Fox, Nitrogenous Constituents of Plants by F. C. Steward and H. E. Street, Growth Substances in Higher Plants by Folke Skoog, and Marine Bacteriology by Claude ZoBell.

The volume is most highly recommended (D. D.)

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